

Anaphylactoid Reactions to Radiocontrast Material

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CHEMISTRY OF CONTRAST AGENTS

Organic, iodinated contrast agents were first successfully administered in 1929 (1). The first generation of contrast agents were hyperosmolar and either mono- or diiodinated pyridones. Several years passed before the second generation of contrast agents, the triiodinated benzoates, were developed. Triiodinated benzoates have been the standard radiographic contrast agents for the past 30 yr.

These agents are iodinated at positions 2, 4, and 6 of the benzene ring. Positions 1, 3, and 5 are left open for substitutions that affect solubility. To achieve an adequate concentration for intravascular use, they require an iodine content of at least 200 mg I/mL. Thus, commonly employed doses of contrast may contain as much as 25–30 g of iodine in a form tightly bound to the benzene ring.

The older of these agents (diatrizoate and iothalamate) are ionic compounds. The cations employed are either sodium; a mixture of sodium, calcium, and magnesium; the sugar meglumine; or a mixture of sodium and meglumine. To achieve a concentration of iodine necessary for adequate urinary tract and vascular opacification, these contrast agents must be administered in forms hypertonic relative to blood.

This hypertonicity (approx $5\times$ that of plasma) results in numerous undesirable side effects. These include sensations of warmth and nausea on injection, pain on inadvertent subcutaneous extravasation, and prolonged discomfort during venography. Thrombophlebitis can also occur. There is *in vitro* evidence of damage to vascular endothelium and sludging of red cells (2,3). Intracoronary injection results in negative inotropic and chronotropic effects, as well as conduction defects (4).

The past decade has witnessed the development of a third generation of contrast agents that are administered in an osmolality much closer to that of plasma. Five agents are available. These are Metrizamide, Iohexol, Iopamidol, Ioversol, and Ioxaglate. Four of these agents, Metrizamide, Iohexol, Ioversol, and Iopamidol, are nonionic monomers. Because they do not ionize in solution, their osmolarity is reduced. Ioxaglate is an ionic dimer. It is more isoosmolar because each molecule of contrast agent has six rather than three iodine molecules, and therefore greater radiopacity per particle in solution is achieved. All of these "isoosmolar" agents provide excellent radiographic opacification with a reduction in many of the side effects noted above (5–7). The frequency with which they produce anaphylactoid reactions has not been established, but it is clear that anaphylactoid reactions do occur to these agents (*see below*). The greatest present disadvantage of isoosmolar agents is their cost.

EPIDEMIOLOGY

Reaction rates for all types of reactions to radiocontrast material (RCM) have been reported to range from 4.63–8.53% (8–22). Anaphylactoid reactions occur in 1% or less of patients receiving RCM. Fatalities have been reported to occur in as many as 0.009% of patients evaluated (11). With these figures in mind, it is quite clear that RCM is one of the most significant causes of anaphylactoid reactions in the world today and probably rivals in frequency those resulting from penicillin.

Reactions occur most commonly between ages 20–50; they are relatively rare in children (17,18,21). Reactions occur with equal frequency in females and males (11,21). They can occur during both

iv and arterial administration (21). Atopy has long been cited as a predisposing factor based on the result of retrospective studies (8,11,17,18,21). However, "allergy" as defined in these studies included any number of diverse reactions, including food intolerances, nonallergic rhinitis and asthma, and nonatopic drug reactions. Therefore, the results of these studies are extremely difficult to evaluate. In one investigation (23) involving smaller numbers of patients, there was no increased incidence of atopy among reactors. However, a recently published study, and the most definitive exam done to date, did find that atopic individuals were at risk for the development of anaphylactoid reactions to radiocontrast material. This study was the first to employ not only historical data, but also skin test data and in vitro testing to assess the presence of atopy (24). Sixty-eight percent of those patients reacting to radiocontrast, compared to 30% of controls, had a positive history of atopic disease. Fifty-six percent of reactors, compared to 24% of controls, had positive immediate hypersensitivity skin tests. Based on these data, the authors concluded that atopic individuals were more susceptible to anaphylactoid reactions to RCM.

THEORIES OF PATHOGENESIS

Any classification of theories of pathogenesis of reactions to RCM is somewhat artificial. For the purpose of discussion, such theories may be classified into four categories: complement activation, direct histamine release from mast cells and basophils, the recruitment of multiple inflammatory mediators (probably via the activation of Factor 12), and antigen-antibody interactions. Discussions of pathogenesis will follow these headings.

Complement Activation

RCM clearly activates the complement cascade. This has been demonstrated both in vitro and in vivo (25-42). Complement activation was first demonstrated in dogs (25). It was later shown that significant falls in serum complement occurred in large percentages of subjects receiving RCM for diagnostic studies (26,29,31,34,36). In vivo reductions occur rapidly. They are demonstrable within 90 s

after iv infusion (37). They are usually short-lived, with serum complement returning to normal after 30 min (37).

Nonetheless, falls in complement do not consistently correlate with the presence of anaphylactoid reactions. Nonreactors can not uniformly be distinguished from reactors on the basis of such falls (29,37,39). However, "baseline" levels of serum complement (CH 50) have been shown to be reduced in a group of reactors compared to controls (30,31). Reactors have also been found to have depressed C1 esterase inhibitor levels in both baseline and postinfusion serum samples (31). On the basis of these observations, it has been hypothesized that reactions occur in patients with ongoing complement utilization (31). However, a prospective analysis of subjects experiencing reactions does not support this contention in that there is no apparent predilection for reactions to occur in patients with diseases involving complement activation (22).

Numerous investigations have attempted to define the mechanism(s) by which RCM induces complement activation. No single mechanism can explain this activation. RCM can induce complement activation via unique interactions not involving the classic or alternative pathways. Activation can occur in serum depleted of C4 (36) and C2 (33), and in agammaglobulinemic serum (33). Activation can occur in spite of the presence of EDTA or EGTA (28,32,33,36). Activation may be nonsequential. That is, simultaneous depression of components of both the alternative and classical pathways has been demonstrated (36). Finally, RCM-induced complement activation can produce a cleavage product of C3, which is not identical to that produced by activation of either the classical or the alternative pathways (32). The exact nature of this nonsequential activation process is unknown. There is evidence, however, to support the contention that activation occurs indirectly via the induction of a lytic enzyme system. This putative enzyme system appears to cleave several complement components simultaneously (nonsequentially) (32,33,36). In support of this postulation is the fact that C3 cleavage occurs only in the presence of serum, and that the cleavage product, as noted above, is distinct from that produced by alternative and classical pathway activation (32,33). It has been suggested that this putative lytic enzyme system responsible for RCM-induced complement activation is the plasminogen activator-plasmin system (36). Recruitment of this system is consis-

tent with the fact that a consumptive coagulopathy can occur during RCM-induced anaphylactoid reactions (38), and that subjects with depressed complement levels can also have fibrin split products in their sera (39).

Ionic and nonionic RCM may activate complement through different mechanisms (40). Ionic RCM has been shown to exert a direct effect on C3 and C4, which did not involve the enlistment of a lytic enzyme system. Ionic RCM produced a conformational change in C3 and C4 leading to products resembling activated C3 and C4. These "activated products" were antigenically related to C3b and C4b, and were able to assemble fluid-phase C3 convertases, but were hemolytically inactive. The formation of these products was not inhibited by EDTA. These "C3b-like" and "C4b-like" molecules were similar to those produced by the action of nitrogen nucleophiles and chaotropes on complement. It was shown that the C3b- and C4b-like components arose via the direct action of RCM on native C3 and C4 molecules at their internal thiolester bonds. Ionic RCM cleaves these bonds, producing C3b-like and C4b-like molecules distinct from those formed during classical or alternative complement activation. Hepatotrophic ionic RCM was more effective than nephrotrophic ionic RCM in causing these changes (40).

In contrast to ionic RCM, a nonionic preparation, metrizamide, did not react with the internal thiolester bonds of C3 and C4, but activated complement through two other pathways. Metrizamide-induced complement activation was inhibited by EDTA. The C3b molecule produced by Metrizamide-induced complement activation was identical to that produced by activation of the alternative complement pathway. Metrizamide failed to exert an effect on C4. Furthermore, Metrizamide effectively prevented the action of the alternative pathway inhibitory system consisting of factors H and I. Thus, it was suggested that Metrizamide's action on complement was via the inhibition of factors H and I, allowing for unrestricted alternative complement pathway activity (40).

Metrizamide also had a less important effect on C2. Although C3 consumption in Metrizamide-treated sera did not occur when EDTA was added (thus preventing alternative pathway activation), total hemolytic activity was reduced in the presence of EDTA. This reduction parallels falls in C2, whereas C1 and C4 are not affected. The mechanism of C2 "activation" was not elucidated (40).

Regardless of the mechanism of complement activation utilized by RCM, the cleavage products so produced are biologically active. In vitro activation is associated with the generation of anaphylatoxic and chemotactic cleavage components (28). In vivo injection during coronary angiography can produce C3a levels between four- and ten-fold normal (41). Seven of 11 patients undergoing angiography demonstrated C3a formation. However, only one patient developed symptoms, and these were mild, not requiring therapy. In another study, a case report, it was postulated that complement activation was responsible for the death of a patient undergoing an iv pyelogram with diatrizoate (42). In this patient, pathology findings were similar to those in patients dying with adult respiratory tract distress syndrome. Granulocytic aggregates were found impacted in microscopic pulmonary arteries and capillaries. It was suggested that these aggregates were the result of complement activation with the formation of anaphylatoxins. Such anaphylatoxin generation was demonstrated in vitro by incubation of diatrizoate with serum (42).

It should be noted that not every investigation has confirmed the observation that RCM is capable of activating complement in vitro. In two investigations (32,43), only iodipamide, and no other agent, was capable of activating complement. In one of these investigations (43), no actual cleavage components of complement were found. There was an illusion of activation with the formation of cleavage products produced by a direct binding of RCM to complement components. This nonspecific binding produced an artificial reduction in the concentration of complement components when these components were measured antigenically (43).

Nonetheless, the weight of evidence, based upon the above studies, supports the contention that RCM is capable of activating complement both in vitro and in vivo. There appear to be multiple activation pathways. Ionic agents may activate complement in a nonsequential fashion. They appear to do so either through the recruitment of a lytic enzyme system or via a direct action on internal thiolester bonds of C3 and C4. Nonionic agents may work through different means, the most important of which may involve the inactivation of factors H and I. The role of complement in the production of anaphylactoid events remains speculative, however. Changes in complement titers cannot be consistently correlated with the induction of anaphylactoid events.

DIRECT HISTAMINE RELEASE FROM MAST CELLS AND BASOPHILS

Because reactions to radiocontrast material are often identical to those produced by classical IgE-mediated anaphylactic reactions, numerous investigators have attempted to define a role for histamine in the production of these reactions (44–67). The majority of these studies have demonstrated RCM's ability to induce histamine release from both basophils and mast cells both *in vitro* and *in vivo* (44–64,66,67). This release process occurs in a dose-dependent fashion (53,54) and does not involve cell death (54). In reactors, it can be specific for the RCM producing the anaphylactoid episode (52,53). RCM-induced histamine release is slower in time-course than that produced by antigen–IgE interaction. It is delayed in onset, usually beginning 10 min after incubation, and is slow to peak, usually doing so 45 min after incubation (55). In these aspects, it resembles the release induced by ionophore (61). RCM-induced histamine release is enhanced by serum, implying a role for anaphylatoxins in the release process (54). Iodine is not necessary for *in vitro* histamine release. Noniodinated diatrizoate is as effective as iodinated diatrizoate in the release process (60). Release occurs with both hyper- and isoosmolar agents (54,62), but in animal models, may be less intense with isoosmolar agents (66,67). Isoosmolar agents have been shown to produce a peculiar biphasic release response (62). Meglumine salts are more effective releasing agents than are sodium salts (62). Release is optimal at 37°C and is calcium-dependent (61). Atopic basophils appear to be more sensitive to RCM than those of non-atopics (60). The basophils of previous reactors appear more sensitive than those who have received RCM without reactions (54).

An interesting aspect of the interaction between diatrizoate and basophils resides in the properties of diatrizoate that cause it to inhibit histamine release because of other agents. When diatrizoate is incubated with basophils under conditions that do not produce release, subsequent incubation of these same cells with releasing agents (antiIgE, F-MET peptide, and calcium ionophore) fails to produce histamine release (61).

This inhibitory or “desensitizing” property of diatrizoate is maximal at 37°C, not related to cell death, and cannot be overcome by increasing calcium concentration, the addition of a nonspecific methyl

donor, or the addition of D20. Thus, it was postulated that diatrizoate was interacting with several enzymatic and cellular functions simultaneously to "desensitize the cell" and inhibit histamine release owing to other agents (61). This peculiar ability of diatrizoate to inhibit histamine release by other agents cannot be explained at this time.

In vivo histamine release has been demonstrated both in animal models (47,59) and in humans (39,45,49,56,63,64). It can occur during both iv and intraarterial administration (39,45,49,56). In animal models, release can be consistently correlated with the production of pathophysiologic events (43,58). In humans, however, such a correlation cannot be consistently demonstrated. In three studies (39,56,64) reactors could not be distinguished from nonreactors by the measurement of intravascular histamine. In another study (63), however, which measured urinary histamine, reactors experienced significant elevations of histamine compared to a nonreactor group. The levels of urinary histamine found in the reactor group were similar to those noted in patients having anaphylactic episodes produced by allergen immunotherapy.

The mechanism by which histamine is produced has not been clarified. Four theories have been advanced:

1. A direct effect on mast cells and basophils via interaction with a cell membrane receptor;
2. The generation of anaphylatoxins secondary to complement activation;
3. Release owing to hyperosmolarity; and
4. Release owing to IgE-antigen interaction.

The most plausible of these theories appears to be the suggestion that there is an interaction between RCM and a cell membrane receptor. Evidence favoring this theory can be summarized as follows:

1. In vitro release may be specific for the RCM producing a reaction in a given individual (52,55), thus suggesting a stoichiometric relationship between a receptor and a prosthetic group on the RCM;
2. In vitro release resembles ionophore-induced release (55); and
3. Release occurs when washed basophils are employed, thus demonstrating complement is not necessary for degranulation (52,55).

As noted, however, no definite stoichiometric relationship could be found between RCM, RCM analogs, and a proposed basophil receptor (54).

The hypothesis that hypertonicity of RCM is responsible for histamine release is supported by several observations. First of all, as noted, many presently employed RCMs are hypertonic, having osmolarities as high as 5–8× that of plasma (68). Hypertonic agents can induce histamine release *in vitro* (69) and hyperosmolarity enhances *in vitro* release resulting from antigen (70). Newer isotonic agents appear to induce reactions less frequently than hypertonic agents (71).

On the contrary, hypertonic agents (not RCM) administered *iv* to rabbits failed to produce the same adverse effect as those caused by RCM of equal osmolarity (58). In addition, *in vitro* histamine release is produced by both isoosmolar and hyperosmolar agents (54,62). Finally the characteristics of *in vitro* release owing to hyperosmolar agents differ from the characteristics of release induced by RCM. These differences exist in regard to time-course of release, calcium dependency, and the optimum temperature for release (61). Thus, the weight of evidence does not favor hypertonicity as a primary cause of histamine release owing to RCM. From the above, it is obvious that RCM can induce histamine release. However, the exact mechanism through which this release occurs has not been clarified.

RECRUITMENT OF MULTIPLE INFLAMMATORY MEDIATORS (MULTI-MEDIATOR ACTIVATION)

RCM produces a number of other biological effects. These effects may contribute to the anaphylactoid episode. RCM can inhibit platelet aggregation (72) and can induce serotonin release from platelets (58). Profound effects are exerted on the clotting system (38,39,73,74). Disseminated intravascular coagulation has been demonstrated in patients experiencing reactions to RCM (74), and fibrin split products can be found in the sera of both reactors and nonreactors receiving RCM (39). RCM binds nonspecifically to serum proteins (75–77) and clotting factors (43). Subclinical bronchospasm can occur during RCM administration (78). A number of different enzyme systems, including acetylcholinesterase, lysozyme, and others, are inactivated by RCM (77,79). RCM infusion can alter myocardial conduction (80) and produce hypocalcemia (37). Red blood

cell structure and flow can be significantly altered (81). Vascular endothelium can be disrupted and damaged by RCM infusion (82). This disruption could, at least theoretically, activate Factor 12, thereby initiating clotting, clot lysis, and kinin formation (83). In keeping with the hypothesis that Factor 12 is key in the production of anaphylactoid events, it has been shown that reactors convert prekallikrein to kallikrein more efficiently and rapidly than do nonreactors (83,84).

Although RCM can produce protean biological effects, it is not possible to collate these into a unifying hypothesis to explain the anaphylactoid reaction. Perhaps the most salient aspect of RCM toxicity involves the disruption of the vascular endothelium. The mechanism of production of endothelial toxicity is unknown, but it may be the result of a combination of the effects of hyperosmolarity (85), direct toxicity (86), and high injection pressures (85). Regardless of the mechanism involved, such disruption might serve as the nidus of inflammation that could ultimately produce cell aggregation and activation of Factor 12. Also of possible importance is the ability of RCM to inactivate various enzyme systems (77,79). Such inactivation could account for its ability to inhibit histamine release to antiIgE, and calcium ionophore (61).

Even if these diverse effects cannot be correlated with the anaphylactoid reaction, it is possible that they are playing a role in the production of other types of untoward reactions, such as the adult respiratory tract distress syndrome (42), and disseminated intravascular coagulation (74).

ANTIGEN-ANTIBODY INTERACTION

Because of the clinical similarity between the RCM-induced anaphylactoid reaction and classical anaphylaxis, it has been postulated that RCM reactions are IgE-mediated. In support of this contention are numerous observations documenting the fact that RCM can be immunogenic (60,87-93). One investigation presented evidence that reactors, but not nonreactors, have specific IgE antiRCM (93). Even though it has been shown that RCM can be immunogenic, however, the characteristics of in vitro-induced

histamine release differ from those of antigen-induced release (61), and the weight of evidence does not support the thesis that reactions are immunologically induced (51,94).

APPROACH TO THE PATIENT AT RISK

From the above discussion it is evident that, in spite of intensive efforts, the pathogenesis of anaphylactoid reactions to RCM remains unclear. Fortunately, however, we are able to deal effectively with the most salient clinical problem, the patient at increased risk.

Patients who have experienced a previous reaction are clearly at risk of a repeat reaction. The exact repeat reaction rate is unknown, but probably approaches 16–30% (95–111). Such repeat reactions can be fatal.

Fortunately, the incidence and severity of recurrent reactions can be significantly reduced by employing pretreatment regimens (95–111). Several pretreatment regimens have been utilized. These include an H1 antagonist alone (95); prednisone alone (98); prednisone plus an H1 antagonist (101); prednisone, an H1 antagonist, plus ephedrine (106); the combination of an H1 and H2 antagonist (111); prednisone plus an H1 antagonist and an H2 antagonist (110); and finally, prednisone plus an H1 antagonist, an H2 antagonist, and ephedrine (110). It appears as if all of these regimens are effective in significantly reducing the incidence of recurrent reactions and in reducing the severity of such reactions. The recurrence rate using these regimens has ranged from about 6–9% (105–107). In addition, the severity of recurrent reactions has been reduced (107,108).

There is little controversy that a standard treatment regimen consisting of prednisone 50 mg by mouth 13 h, 7 h, and 1 h before the procedure, diphenhydramine 50 mg intramuscularly 1 h before the procedure, and ephedrine 25 mg by mouth 1 h before the procedure (when not contraindicated) is a highly effective and safe pretreatment regimen. There has been some controversy regarding the efficacy of the addition of an H2 antagonist to this regimen. In one study, the addition of cimetidine reduced the efficacy of the

Table 1
Pretreatment Protocol for Prevention
of Anaphylactoid Reactions to Previous Reactors

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1. Prednisone 50 mg by mouth, 13 h, 7 h, and 1 h prior to procedure
 2. Diphenhydramine 50 mg intramuscularly 1 h prior to procedure
 3. Ephedrine 25 mg by mouth 1 h prior to procedure
 4. An H2 antagonist (e.g., ranitidine or cimetidine 300 mg) by mouth 3 h prior to procedure
 5. Use an "iso-osmolar" agent
 6. Explain risk; obtain permission from patient
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pretreatment protocol (107). Other investigators have found that the combination of an H1 and H2 antagonist is superior to an H1 antagonist alone (111). In one study, there was no difference between patients treated with the combination of an H1 and H2 antagonist and those treated with an H1 antagonist alone (110). However, based upon the observations that the pathophysiology of anaphylaxis is clearly related to the stimulation of both H1 and H2 receptors (112,113), and the combination of an H1 and H2 antagonist has been shown to be superior to an H1 antagonist alone in the prevention of reactions to morphine (114) and plasma expanders (115), it would seem reasonable to add an H2 antagonist to the preventive protocol. The weight of evidence in the literature supports this contention.

In addition to using the above medication regimen, it is wisest to use an isoosmolar agent in patients who have demonstrated previous reactions. It is clear that side effects, including anaphylactoid reactions, occur less frequently with isoosmolar agents than with hypertonic agents (116–122). However, it should clearly be noted that anaphylactoid reactions can occur as a result of the administration of isoosmolar agents (123). Thus, even when an isoosmolar agent is used, pretreatment is still necessary.

Based upon the above observations, an ideal pretreatment regimen would therefore, in most cases, consist of the administration of prednisone, an H1 antagonist, an H2 antagonist, ephedrine, and an isoosmolar agent. The exact pretreatment protocol is seen in Table 1.

From the above data, it is apparent that a pretreatment protocol is highly effective in decreasing reaction rates and reducing the severity of repeat reactions in high-risk patients. However, a word of caution must be interjected. The pretreatment protocols noted above are solely for the prevention of *anaphylactoid reactions*. Pretreatment of other types of life-threatening reactions has not been adequately evaluated. It is therefore incumbent on the physician to determine the nature of the previous reaction. Of particular note is the example of "shock lung" (adult respiratory tract distress syndrome or noncardiogenic pulmonary edema), which can be induced by RCM. There are instances (124–126) where standard pretreatment protocols have failed to prevent reactions. In at least two of these (124,125), the reactions were characterized by apparent noncardiogenic pulmonary edema with adult respiratory tract distress syndrome. In both these cases, the reactions were severe. Thus, in instances where the initial reaction was consistent with noncardiogenic pulmonary edema, the pretreatment protocol could not be trusted to prevent a recurrence.

A graded, provocative challenge has also been proposed for the management of the previous reactor, high-risk patient (127,128). Such provocative dosage regimens were originally abandoned because of the observation that reactions could occur at very low doses given as "test doses" (128). However, when radiocontrast was highly diluted and administered using a gradually increasing dosage regimen, successful administration has been accomplished. This method entails the administration of progressively stronger concentrations at 10- to 15-min intervals until full-strength RCM is given. At the conclusion of the uneventful graded administration, the RCM study is performed. This procedure has been effective in preventing serious reactions by producing minor reactions during provocative testing, and thereby allowing the physician to abort the procedure before the advent of severe symptoms. The procedure probably utilizes the fact that RCM reactions are, like other drug reactions, dose-dependent.

There are obvious disadvantages to this provocative testing procedure. These include the time required (about 1.5 h) to complete the procedure and the necessity for a physician's presence throughout the course of administration. Furthermore, because the

pretreatment schedule has been so successful in reducing the incidence and severity of recurrent episodes, the provocative testing procedure is not indicated in the vast majority of instances. When the previous reaction has been life-threatening, however, the physician may opt to use a combination of the provocative dosage regimen and the pretreatment regimen noted above.

Occasionally, a high-risk patient must undergo an emergency radiographic procedure when there is no time to use the pretreatment regimen noted above, which requires 13 h. For this purpose, an emergency pretreatment protocol has been established (129).

This procedure consists of the administration of hydrocortisone 200 mg iv immediately and every 4 h until the procedure is performed. Diphenhydramine 50 mg intramuscularly is also given 1 h before the procedure. Although there are no published data to validate the addition of ephedrine or an H₂ antagonist in this situation, it is likely that they would be helpful. An isoosmolar agent should of course be used.

It is important to note that anaphylactoid reactions to RCM can occur when these agents are administered by nonvascular routes. For example, reactions have occurred during histosalpingograms (130) and retrograde pyelograms (131). Thus, previous reactors undergoing these procedures should be pretreated. However, this holds true only when the agent employed utilizes a tri-iodinated benzene ring. Pretreatment is not necessary for myelography when an older, oil-based, nonbenzene ring agent, such as iophendylate, is employed. When isotonic, tri-iodinated benzene ring agents, such as metrizamide, are employed, pretreatment is necessary.

It should be emphasized that reactions can occur in pretreated subjects. It is therefore imperative to document the essential indication for the study and explain the risk to the patient. Of course, proper equipment must be available to treat any anaphylactoid reaction that might occur.

Many patients requiring intravascular studies employing RCM are taking β -adrenergic blocking agents. The question often arises as to whether or not to discontinue the use of these agents prior to the performance of a study in a previous reactor. Although there is evidence in the literature to indicate that the frequency of such reactions in patients taking β blockers is not increased (107,132), it is still logical to presume that any reaction occurring in a patient on a β -adrenergic blocking agent might be more difficult to treat. It is,

therefore, our practice to discontinue these agents prior to the performance of the procedure if at all possible.

Because of the proven efficacy of the pretreatment protocols mentioned above, it has been suggested that all patients receiving RCM be pretreated. With the advent of isoosmolar agents, which produce reactions less frequently, the interest in pretreating all subjects receiving ionic RCM has grown. This is because there is a great debate over the cost/benefit of the routine employment of isoosmolar agents (133). Such agents are considerably more expensive than ionic agents in the United States. Thus, radiology departments have been forced to make the decision to use much more expensive agents or to place patients receiving RCM at a possibly increased risk of reactions. A pretreatment protocol that would safely and less expensively equalize reaction rates would be highly desirable. It has been shown that methylprednisolone pretreatment of all patients receiving RCM, regardless of whether or not they had experienced a previous reaction, may accomplish this (134,135). Methylprednisolone given in a dose of 32 mg 12 and 2 h before the procedure successfully reduced reaction rates in patients receiving ionic agents. This of course can be accomplished with much less cost than the routine use of isotonic RCM. At the time of the preparation of this manuscript, there was an ongoing study utilizing a combination of cimetidine and hydroxyzine given to all patients receiving RCM in an attempt to further evaluate a routine pretreatment protocol. Whether or not such routine pretreatment will be widely utilized is unknown.

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