PATIENT SELECTION AND PREPARATION STRATEGIES

General Considerations

The approach to patients about to undergo a contrast-enhanced examination has three general goals: 1) to assure that the administration of contrast is appropriate for the patient and the indication; 2) to minimize the likelihood of a contrast reaction; and 3) to be fully prepared to treat a reaction should one occur (see Table 4). Achieving these aims depends on obtaining an appropriate and adequate history for each patient, preparing the patient appropriately for the examination, having equipment available to treat reactions, and ensuring that expertise sufficient to treat even the most severe reactions is readily at hand. Although mild reactions to contrast media are relatively common, they are almost invariably self-limited and of no consequence. Severe, life-threatening reactions, although rare, can occur in the absence of any specific risk factors with any type of media.

The history obtained should focus on identification of factors that may indicate either a contraindication to contrast media use or an increased likelihood of a reaction.

Risk Factors for Adverse Intravenous Contrast Material Reactions

Allergy: With regard to specific risk factors, a history of a prior allergy-like reaction to contrast media is associated with an up to five fold increased likelihood of the patient experiencing a subsequent reaction [1]. Additionally, any allergic diathesis predisposes individuals to reactions. This relationship is a difficult one to define, since many individuals have at least a minor allergy, such as seasonal rhinitis, and do not experience reactions. True concern should be focused on patients with significant allergies, such as a prior major anaphylactic response to one or more allergens.

The predictive value of specific allergies, such as those to shellfish or dairy products, previously thought to be helpful, is now recognized to be unreliable [2-3] A significant number of health care providers continue to inquire specifically into a patient's history of "allergy" to seafood, especially shellfish [4]. There is no evidence to support the continuation of this practice [4-5].

Any patient who describes an "allergy" to a food or contrast media should be questioned further to clarify the type and severity of the "allergy" or reaction, as these patients could be atopic and at increased risk for reactions [2]. Most forms of atopy result in a 2 to 3 times likelihood of contrast reaction compared with non-atopic patients [2]. However, considering the rarity of severe life-threatening anaphylaxis, this level of incremental risk remains low and should be considered in the context of risk versus benefit.

Asthma: A history of asthma may indicate an increased likelihood of a contrast reaction [1,6]

Renal Insufficiency: Another specific risk category is renal insufficiency [7]. For this reason, each patient should be questioned whether he or she has a history of renal dysfunction. Discussion of contrast-induced nephrotoxicity (CIN) and nephrogenic systemic fibrosis (NSF) can be found in the Chapters on Contrast Nephrotoxicity and NSF.

Cardiac Status: Patients with significant cardiac disease may be at increased risk for contrast reactions. These include symptom-matic patients (e.g., patients with angina or congestive heart failure symptoms with

minimal exertion) and also patients with severe aortic stenosis, primary pulmonary hypertension, or severe but well-compensated cardiomyopathy. In all such patients, attention should be paid to limiting the volume and osmolality of the contrast media.

Anxiety: A general category that deserves attention is emotional state. There is anecdotal evidence that severe adverse effects to contrast media or to procedures can be mitigated at least in part by reducing anxiety. It may be useful, therefore, to determine whether a patient is particularly anxious and to reassure and calm that patient before contrast injection. This issue was studied with reference to anxiety thought to be generated by informed consent of risks associated with intravenous (IV) contrast procedures [8]. Using a standardized anxiety index, it was concluded that the majority of patients who were and were not informed had equally elevated anxiety, and there was no increase in adverse reactions in the informed group.

Miscellaneous Risk Factors: There are several other specific risk factors that deserve attention.

Paraproteinemias, particularly multiple myeloma, are known to predispose patients to irreversible renal failure after high-osmolality contrast media (HOCM) administration due to tubular protein precipitation and aggregation; however, there is no data predicting risk with the use of low-osmolality or iso-osmolality agents.

Age, apart from the general health of the patient, is not a major consideration in patient preparation [1]. In infants and neonates, contrast volume is an important consideration because of the low blood volume of the patient and the hypertonicity (and potentially detrimental cardiac effects) of even nonionic monomeric contrast media. Gender is not considered a risk factor for IV contrast injection.

Some retrospective case control studies suggest a statistically significant risk that the use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions, and reduces the responsiveness of treatment of anaphylactoid reactions with epinephrine [9].

Others have suggested that sickle cell trait or disease increases the risk to patients; however, in neither case is there evidence of any clinically significant risk, particularly after the injection of low-osmolality contrast media (LOCM) [10].

Concomitant use of certain intra-arterial injections, such as papaverine, is believed to lead to precipitation of contrast media during arteriography. There have been reports of thrombus formation during angiography using nonionic as opposed to ionic agents. In both cases, there are in-vitro studies that suggest possible explanations.

Some patients with pheochromocytoma develop an increase in serum catecholamine levels after the IV injection of HOCM. A subsequent study showed no elevation of catecholamine levels after the IV injection of nonionic contrast media [11]. Direct injection of either type of contrast medium into the adrenal or renal artery is to be avoided, however, as this may cause a hypertensive crisis.

Some patients with hyperthyroidism or other thyroid disease (especially when present in those who live in iodine-deficient areas) may develop iodine-provoked delayed hyperthyroidism. This effect may appear 4 to 6 weeks after the IV contrast administration in some of these patients. This can occur after the administration of any iodinated contrast media. It is usually self-limited.

Patients with carcinoma of the thyroid deserve special consideration before the IV or oral administration of iodinated contrast media (ionic or nonionic). Uptake of I-131

in the thyroid becomes moderately decreased to about 50% at one week after iodinated contrast injection but seems to become normal within a few weeks. Therefore, if systemic radioactive iodine therapy is part of planned treatment, a pretherapy diagnostic study of the patient using an iodinated radiographic contrast medium (intravascular or oral) may be contraindicated; consultation with the ordering clinician prior to contrast administration is recommended in these patients.

Intravenous injections may cause heat and discomfort but rarely cause pain unless there is extravasation. Intra-arterial contrast injections into peripheral vessels in the arms, legs, or head can be quite painful, particularly with HOCM. For such injections, iso-osmolality contrast media (IOCM) are associated with the least amount of discomfort.

Premedication

The primary indication for premedication is pretreatment of "at-risk" patients who require contrast media. In this context, "at risk" means at higher risk for an acute allergic-like reaction.

The etiological mechanisms of anaphylactoid contrast reaction are incompletely understood as well as the basis of prevention with the use of corticosteroids [12]. Approximately 90% of such adverse reactions are associated with direct release of histamine and other mediators from circulating basophils and eosinophils. It is now generally accepted that most adverse allergy-like reactions are not associated with the presence of increased IgE and, therefore, unlikely to be truly allergic. However, some studies show definite evidence of IgE mediation [13]. No antibodies to IV contrast media have been consistently identified, and according to skin testing and basophil activation, IgE-mediated allergy is uncommon, occurring in 4% of patients having anaphylaxis symptoms [14]. Pathophysiologic explanations include activation of mast cells and basophils releasing histamine, activation of the contact and complement systems, conversion of L-arginine into nitric oxide, activation of the XII clotting system leading to production of bradykinin [10], and development of "pseudoantigens" [15].

Considerable evidence exists in the medical literature that radiographic contrast media reactions arise from mediators released by circulating basophils. Dose response studies in humans of the suppression of whole blood histamine and basophil counts by IV methylprednisone [16] show a reduction in circulating basophils and eosinophils by the end of the first postinjection hour, reaching statistical significance compared with controls by the end of the second hour, and maximal statistical significance at the end of 4 hours. The reduction of basophils is greater than eosinophils. A reduction of histamine in sedimented leukocytes is also noted at 4 hours. Many of these effects reach their maximum at 8 hours.

The foregoing may provide some rationale for the use of IV steroids for "at risk" patients in emergency situations. Although some corticosteroid preventative effect may be gained as quickly as 1 hour after IV injection of corticosteroids, the experimental data would support a much better prophylactic effect if the examination can be delayed for at least 4 to 6 hours after giving premedication [10,17-18]. If this time interval is not clinically possible, some would omit the use of corticosteroids entirely and give only H1 blockers prior to injection of contrast [17]. However, it should be emphasized that no clinical studies have unequivocally demonstrated prevention of contrast reactions using short-term IV corticosteroid pre-medication.

The osmolality of the contrast agent as well as the size and complexity of the molecule has potential influence on the likelihood of contrast reactions. Hyper-osmolality is associated with the stimulation of release of

histamine from basophils and mast cells. Increase in the size and complexity of the contrast molecule may potentiate the release of histamine [19-20]. There is some evidence to suggest that nonionic monomers also produce lower levels of histamine release from basophils compared with high-osmolality ionic monomers, low-osmolality ionic dimers and iso-osmolality nonionic dimers [20]. A large nonrandomized nonblinded study suggests significantly greater safety of nonionic contrast agents [1]. Similar safety margins have been claimed in other nonrandomized trials [21]; however, no definitive unbiased randomized clinical trials exist that demonstrate significant reduction in severe reactions and fatality [21]. Low-osmolality contrast agents also reduce the non-idiosyncratic physiologic reactions that are not related to allergy. For these reasons there is general agreement that the safety margin for low-osmolality contrast agents is better than that for ionic high-osmolality agents.

Before deciding to premedicate an "at risk" patient, some consideration should be given to the goals of such premedication. Ideally, one would like to prevent all contrast reactions, including minor, moderate, and severe ones. However, it is most important to target premedication to those who, in the past, have had moderately severe or severe reactions requiring treatment. Unfortunately, studies have thus far indicated that the main contrast reactions that benefit from premedication are minor ones requiring no or minimal medical intervention [18]. No randomized controlled clinical trials have demonstrated premedication protection against severe life-threatening adverse reactions [10,22-23]. But this may be attributed to the rarity of life-threatening reactions to contrast and the prohibitive numbers of subjects necessary for enough statistical power to demonstrate any beneficial effect of premedication in preventing the most severe contrast reactions.

Risk of Corticosteroids: Although the risk of a few doses of oral corticosteroids is extremely low [17], precautions must be taken when administering a short course of steroids to some patients. Corticosteroids should be used with caution in patients with uncontrolled hypertension, diabetes [24], tuberculosis, systemic fungal infections, peptic ulcer disease or diverticulitis [17]**.** The relative risk for the use of corticosteroids compared to the likelihood of severe or fatal contrast reaction must be considered. Anaphylactoid reactions to oral glucocorticoids have been rarely reported [36].

In comparison, there have been more frequent reports of serious reactions to IV injections of frequently used corticosteroids [17,25-29]. The most common offenders are the succinate esters of methylprednisolone sodium (Solu-Medrol®) [26,29] and hydrocortisone sodium succinate (Solu-Cortef®) [30]. Some have suggested that non-succinate glucosteroids, such as betamethasone or dexamethasone sodium sulfate (Decadron®), may be safer for intravenous use [29,31], based on follow-up skin prick tests on patients showing anaphylactic symptoms. Cross reactivity of topical and systemic steroids has been described in asthmatics resulting in bronchospasm after injecting the latter [30]. Increased risk for adverse reactions to corticosteroids has been seen more commonly in patients with asthma, particularly if those patients also have acetylsalicylic acid/nonsteroidal anti-inflammatory drug intolerances [26,30].

Pretesting: Preliminary intradermal skin testing with contrast agents is not predictive of adverse reactions, may itself be dangerous, and is not recommended [13-14,32].

Premedication strategies

Oral administration of steroids is preferable to IV administration, and prednisone and methylprednisolone are equally effective. It is preferred that steroids be given beginning at least 6 hours prior to the injection of contrast media regardless of the route of steroid administration whenever possible. It is unclear if administration for 3 hours or fewer prior to contrast reduces adverse reactions. Dunsky et al [16] experimentally established a theoretical scientific basis for such a strategy, but actual demonstration of clinical effects is not, to date, proved. Supplemental administration of an H-1 antihistamine (e.g., diphenhydramine), orally or intravenously, may reduce the frequency of urticaria, angioedema, and respiratory symptoms. Additionally, ephedrine administration has been suggested to decrease the frequency of contrast reactions, but the use of this medication is not advised in patients with unstable angina, arrhythmia, or hypertension. In fact, inclusion of ephedrine in a routine premedication protocol is not recommended. In one clinical study, addition of the H-2 antihistamine cimetidine to the premedication protocol resulted in a slight increase in the repeat reaction rate [33].

Specific Recommended Premedication Regimens

Several premedication regimens have been proposed to reduce the frequency and/or severity of reactions to contrast media.

Elective Premedication

Two frequently used regimens are:

1. Prednisone – 50 mg by mouth at 13 hours, 7 hours, and 1 hour before contrast media injection, *plus*

   Diphenhydramine (Benadryl®) – 50 mg intravenously, intramuscularly, or by mouth 1 hour before contrast medium [12]

   or

2. Methylprednisolone (Medrol®) – 32 mg by mouth 12 hours and 2 hours before contrast media injection. An anti-histamine (as in option 1) can also be added to this regimen injection [34]. If the patient is unable to take oral medication, 200 mg of hydrocortisone intravenously may be substituted for oral prednisone in the Greenberger protocol.

Emergency Premedication (In Decreasing Order of Desirability)

1. Methylprednisolone sodium succinate (Solu-Medrol®) 40 mg or hydrocortisone sodium succinate (Solu-Cortef®) 200 mg intravenously every 4 hours (q4h) until contrast study required plus diphenhydramine 50 mg IV 1 hour prior to contrast injection [35].

2. Dexamethasone sodium sulfate (Decadron®) 7.5 mg or betamethasone 6.0 mg intravenously q4h until contrast study must be done in patent with known allergy to methylpred-nisolone, aspirin, or non-steroidal anti-inflammatory drugs, especially if asthmatic. Also diphenhydramine 50 mg IV 1 hour prior to contrast injection.

3. Omit steroids entirely and give diphenhydramine 50 mg IV.

Note: IV steroids have not been shown to be effective when administered less than 4 to 6 hours prior to contrast injection.

Changing the Contrast Agent to be Injected

In patients who have a prior, documented contrast reaction, the use of a different contrast agent, has been advocated and may sometimes be protective [36]. However, a change from one to another low-osmolality agent generally appears to provide little or no benefit [37]. An optional switch to a different agent may be combined with a pre-medication regimen.

[Note: For a summary of patient preparation strategies, see the table following the references below.]

Breakthrough Reactions

Studies to date have demonstrated a decrease in overall adverse events after steroid premedication before contrast injection, but no decrease in the incidence of repeat severe adverse events [34]. This may be due to the infrequency of severe life-threatening reactions to iodinated contrast. Frequency and severity of repeat contrast reactions in premedicated patients (so-called breakthrough reactions) was recently studied [37-38] resulting in several important conclusions: 1) Breakthrough reaction severity, signs, and symptoms are most often similar to the index reaction; 2) The majority of low-osmolality contrast injections in premedicated patients with a prior breakthrough reaction will not result in a repeat breakthrough reaction; 3) Patients with a mild index reaction have an extremely low risk of developing a severe breakthrough reaction; 4) Patients with a moderate or severe index or breakthrough reaction are at higher risk for developing another moderate or severe reaction should breakthrough occur; 5) Severe allergies to any other substance (which includes IV iodinated contrast) are associated with a somewhat higher risk of developing a moderate or severe breakthrough reaction. This is also true of patients with more than four allergies, any drug allergy, and chronic use of oral corticosteroids [37].

Other considerations

No premedication strategy should be a substitute for the preadministration preparedness discussed in this manual. Contrast reactions occur despite premedication prophylaxis [38]. The radiologist must be prepared and able to treat these reactions. Most commonly, a repeat reaction will be similar to the patients' initial reaction; however, there is a chance that a recurrent reaction will be more or less severe [38].

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