

## ADVERSE EFFECTS OF IODINATED CONTRAST MEDIA

The general frequency of adverse events related to the administration of contrast media has decreased considerably with changes in usage from high-osmolality contrast media (HOCM) to low-osmolality contrast media (LOCM). While the incidence of mild and moderate reactions has decreased, severe and life-threatening adverse events continue to occur unpredictably, and appropriate training of, and vigilance by, healthcare workers are necessary in areas where contrast media are administered.

The majority of adverse side effects are mild non-life-threatening events that require only observation, reassurance, and support. Severe adverse side effects, however, may have a mild or moderate prodrome. Nearly all life-threatening reactions occur immediately or within the first 20 minutes after contrast media injection.

The effects of dose, route, and rate of delivery of contrast media on the incidence of adverse events are not entirely clear. Studies have shown that a “test injection” does not decrease the incidence of severe reactions and may actually increase it. Any intravascular contrast media administration, regardless of route, may result in an adverse event, ranging from mild discomfort to a severe, life-threatening reaction.

### Pathogenesis Mechanisms

Presentations appear identical to an anaphylactic reaction to a drug or other allergen, but since an antigen-antibody response has not been identified in most reacting patients, such a reaction is classified as “anaphylactoid” or as “non-allergic anaphylactic”. Treatment, however, is identical to that for an allergic anaphylactic reaction.

The precise pathogenesis of most adverse events occurring after the administration of contrast media is unclear. There are multiple potential mechanisms. Some reactions may involve activation, deactivation, or inhibition of a variety of vasoactive substances or mediators. Histamine release must have occurred when patients develop urticaria, but the precise cause and pathway of histamine release are not known.

Physiologic mechanisms may relate to the specific chemical formulation of the contrast media, most notably chemotoxicity and hypertonicity, or to binding of the small contrast media molecule to activators. Patient anxiety may contribute to adverse events. Additives or contaminants such as calcium-chelating substances or substances leached from rubber stoppers in bottles or syringes have been suggested as contributory on some occasions.

In general, accurate prediction of a contrast reaction is not yet possible, although it is clear that certain patients are at increased risk of a reaction.

In some cases, the cause of an adverse event can be identified. The etiology of cardiovascular effects, for example, is complex but to some extent definable. Some effects, such as hypotension and tachycardia, have been thought by some to be related to hypertonicity.

Others, such as the negative inotropy and chronotropy that occur with direct coronary injection, are related to both increased osmolality and ionic concentration. Pulseless electrical activity, with associated cardiac arrest, has been shown to result from a sudden drop in serum-ionized calcium, which in turn may be caused by the specific contrast formulation or an additive.

The incidence and severity of such events seem to decrease with the use of low-osmolality and isotonic contrast media.

Further, cardiovascular effects are more frequent and more significant in patients with underlying cardiac disease. For example, patients with left heart failure are less able to compensate for the osmotic load and the minor negative chronotropic effects of contrast media, because of the high osmolality of some contrast media and because of the volume load. As a result, there is an increased risk of developing acute pulmonary edema. Patients with an acute increase in pulmonary vascular resistance, and thus an acute increase in right heart pressure (e.g., patients with massive pulmonary embolism), have an increased risk of developing right heart failure that may be irreversible.

Vasovagal reactions are relatively common and characterized by hypotension with bradycardia. Pathogenesis is unknown, but the response is thought to be the result of increased vagal tone arising from the central nervous system. The effects of increased vagal tone include depressed sinoatrial and atrioventricular nodal activity, inhibition of atrioventricular conduction, and peripheral vasodilatation. Vasovagal reactions are related to anxiety and can occur while consent is being obtained, with placement of a needle or catheter for injection, or with the administration of contrast media via any route. Such reactions generally present with a feeling of apprehension and accompanying diaphoresis.

Most vagal reactions are mild and self-limited, but should be treated and observed closely until they resolve fully, as they may progress to cardiovascular collapse or be associated with angina or seizure secondary to clinically significant hypotension. (See Table 6 – Management of Acute Reactions in Adults.)

Obtaining a focused patient medical history prior to the administration of contrast media

is critically important. Prior reaction to contrast injection is the best predictor of a recurrent adverse event. It is not an absolute indicator, however, since the incidence of recurrent reactions may range from 8% to perhaps as high as 30%. Pre-existing medical conditions can also foreshadow adverse events. Urticarial reactions are more frequent in patients with a strong history of active allergies. Bronchospasm is a common reaction among patients with active asthma. Hemodynamic changes are more common among patients with significant cardiovascular disease, such as aortic stenosis or severe congestive heart failure.

It is very important that all personnel who administer contrast media be prepared to recognize the variety of adverse events that may occur, monitor the patient, and institute the appropriate measures should treatment of an adverse reaction become necessary. These measures may range from notifying the radiologist, to administering medication, to calling a code. Knowledge about the varying adverse effects of contrast media is important, as it will guide the choice of therapy.

### **Special Circumstances**

Drug package inserts suggest precautions are necessary to avoid adverse events in patients with known or suspected pheochromocytoma, thyrotoxicosis, dysproteinemias, myasthenia gravis, or sickle cell disease. There are scant data, however, to support the need for specific precautions in these patients when low-osmolality contrast media is used. (See the Chapter on Patient Selection and Preparation Strategies.)

### **Types of Reactions**

1. Mild
2. Moderate
3. Severe
4. Organ-specific (see Table 2)

Reactions are most often mild but rarely can be life-threatening. Prediction of occurrence

or severity is impossible, although there are some known risk factors, and anticipation and vigilance are critical. In general, it is not possible to classify the etiology of an adverse event following contrast media administration, but it is possible to clarify and classify severity and begin supportive measures.

### *Mild Reactions*

Some reactions, specifically nausea and vomiting, increase in incidence with increasing osmolality.

The frequency of urticarial reactions was high with the use of HOCM. Urticarial reactions are almost always mild, although it can progress to moderate severity. Mild reactions do not require treatment, but, as noted, they may presage or evolve into a more severe reaction. Any patient with any reaction should, therefore, be observed for 20 to 30 minutes, or as necessary, to ensure clinical stability and recovery.

Pain on injection, particularly with injection into the arteries of the lower extremities or into the external carotid arteries, is largely a function of hypertonicity. It is, therefore, much decreased in both incidence and severity with the use of low-osmolality contrast agents and further decreased with the use of iso-osmolality agents. Similarly, sensations of warmth or flushing are an unpleasant physiologic response of very short duration and not indicative of an adverse event.

### *Moderate Reactions*

Moderate adverse events, by definition, are not immediately life-threatening (although they may progress to be so) but often require treatment. These events include symptomatic urticaria, vasovagal reaction, mild bronchospasm, and tachycardia secondary to transient mild hypotension. Moderate reactions require close monitoring until they resolve completely. Treatment may include diphenhydramine for symptomatic hives,

use of a beta-agonist inhaler for bronchospasm, or leg elevation and/or fluid therapy for hypotension. Vital signs should be obtained in any patient suspected of having a moderate reaction. It is also appropriate to consider securing intravenous (IV) access and providing oxygen.

### *Severe Reactions*

Severe adverse events are potentially or immediately life-threatening. Although they are rare, it is imperative that all personnel who administer contrast media be aware that they occur unpredictably and that they require prompt recognition and treatment. Patients may initially experience a variety of symptoms and signs, ranging from anxiety to respiratory distress, diffuse erythema, or sudden cardiac arrest.

Complete cardiopulmonary collapse requires cardiopulmonary resuscitation and advanced specialized life-support equipment and trained personnel. Cardiopulmonary collapse may occur very rapidly, so all patients receiving IV contrast must be observed closely during the procedure. Since the outcome of cardiopulmonary arrest worsens as the response time increases, prompt recognition of such reactions and rapid institution of treatment are crucial.

Severe adverse events also include profound vasovagal reactions, moderate and severe bronchospasm, laryngeal edema, seizure, and severe hypotension. Pulmonary edema may also occur, particularly, but not exclusively, in patients with underlying congestive heart failure.

### *Organ-Specific Effects*

Some organ-specific adverse effects have been noted above. They include pulseless electrical activity (PEA), pulmonary edema, and seizures. The effect of extravasation of contrast during IV administration is generally mild, particularly if low-osmolality contrast media is used, and specific therapies are dealt with elsewhere.

Venous thrombosis can occur in response to an infusion of contrast media. This is related to direct vascular endothelial damage and is more of a problem with HOCM. Contrast media are known to have an effect not only on vascular endothelial function but also on thrombosis and hemostasis. These complex interactions in general are not thought to be major or significant. Contrast media are also known to cause some alteration in red blood cell deformability and in platelet function, but these effects are not thought to be clinically relevant.

Renal effects of contrast media are discussed in the Chapter on Contrast Nephrotoxicity.

In summary, contrast media, acting through various poorly understood mechanisms, can be associated with a variety of adverse events. These events range from trivial to profound and reliable prediction of such reactions is not currently possible. The health care team should be knowledgeable about specific adverse events, risk factors, and signs and symptoms, as well as the need for routine thoughtful patient observation. Personnel must be similarly prepared for expeditious and appropriate treatment when indicated.

### **Delayed Reactions to Contrast Media**

Reactions that are not acute have long been a source of concern with both iodinated and gadolinium-based contrast media. Currently, delayed reactions to gadolinium media in the form of nephrogenic systemic fibrosis (NSF) are a major concern, and are dealt with in detail elsewhere in this manual.

Many different symptoms and signs have been reported as delayed reactions associated with iodinated contrast media. Some relatively common ones are nausea, vomiting, drowsiness, headache, and pruritus without urticaria, all of which are self-limited and usually do not require therapy. Delayed cardiopulmonary arrest has also been reported, but this and other severe

systemic reactions are probably related to etiologies other than the contrast media.

Currently, other than contrast-induced nephropathy, the delayed reactions to contrast media that are of most frequent concern are the cutaneous ones. These are important for several reasons: they occur more often than is generally recognized; they may recur; they may have serious sequelae; and, perhaps most importantly, they are often ascribed to causes other than contrast media.

The incidence of delayed adverse cutaneous reactions has been reported to range from 0.5% to 9%. Some are moderate to severe in distribution and associated symptoms. Delayed cutaneous reactions are more common in patients treated with interleukin-2 (IL-2) therapy.

The onset of delayed cutaneous reactions ranges from 3 hours to 7 days following the administration of a contrast agent. For several reasons (lack of awareness of such adverse events, usual practice patterns, relatively low frequency of serious outcomes), they are often not brought to the attention of the radiologist and are ascribed to other causes because contrast agents have a biologic half-life of less than one hour, are too small to function unbound as antigens, and are minimally protein bound.

Delayed cutaneous reactions present with an exanthem that varies widely in size and distribution. The manifestations are often macular but may be maculopapular or pustular or may resemble angioneurotic edema, and are usually associated with pruritus. They are generally self limited and require only minimal symptomatic therapy. They may, however, progress to severe symptomatology with wide distribution. Cases have been reported that resemble Stevens-Johnson syndrome, toxic epidermal necrolysis, or cutaneous vasculitis, and one fatality has even been described. When the rash is limited, symptomatic therapy such as corticosteroid creams can be used; if it is

progressive or widespread, or if there are significant associated symptoms, consultation with allergy or dermatology services is an appropriate early step.

These adverse events are also unusual in that there is a high rate of recurrence, particularly if the same contrast medium is used but also with a different specific contrast agent. The true recurrence rate is not known, but anecdotally it is greater than 25%. Delayed cutaneous reactions are not, however, associated with other acute adverse events such as bronchospasm or laryngeal edema. The etiology, as with most significant contrast-related complications, is not clear. Because of the tendency to recur and because of the associated symptomatology, these reactions are thought to be T-cell mediated. The effectiveness of prophylaxis, particularly with oral corticosteroids, is unknown.

In summary, delayed cutaneous reactions are relatively frequent and are often mistakenly thought to be caused by another inciting media, in part because of the physiology of contrast media, and in part because many radiologists are (not surprisingly) unaware that such reactions occur. These adverse events appear to be true delayed-hypersensitivity reactions and tend to recur if contrast medium is administered again, particularly if the same agent is used. Their onset ranges from three hours to a week after contrast administration. These reactions should be followed closely, documented thoroughly, and treated symptomatically with the realization that symptoms and signs may occasionally become clinically significant.

### **Other Adverse Effects**

Iodide “mumps” (salivary gland swelling) and a syndrome of acute polyarthropathy are two delayed reactions that can occur with either high-osmolality or low-osmolality contrast media and that may be more frequent in patients with renal dysfunction.

**Suggested Reading** (Articles that the Committee recommends for further reading on this topic are provided here.)

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