

### **Adverse reactions to iodinated contrast media**

Iodinated contrast agents are among the most commonly administered drugs worldwide. In United State more than 80 million CT examinations are performed annually and almost half are performed with iodinated contrast agents.<sup>1</sup> Iodinated contrast media are used in imaging techniques to enhance the differences between body tissues on images. These have been in use since 1950 and in current era almost all medical imaging modalities use contrast agents to improve image interpretation.

Iodinated contrast agents are classified on the basis of their osmolar characteristics. Hyperosmolar contrast agents (HOCA) are 5-6 times more hyperosmolar than plasma. These are ionic, monomeric derivatives of tri-iodinated benzoic acid and its molecule dissociates in solution into anion and cation. The anion is iothalamate, diatrizoate or metrizoate while cation is sodium, meglumine or mixture of two. In middle of 1980s, low osmolality contrast agents (LOCA) were introduced which are 2-2.5 time more hyperosmolar than plasma. LOCAs are either ionic dimers (like ioxaglate) or non-ionic monomers which don't dissociate in solution (like iohexol, ioversol, iopamidol). Iso-osmolar contrast agent (IOCA) has osmolality equal to plasma and iodixanol is the only agent which non-ionic dimer.

Due to overwhelming use of iodinated contrast agents in clinical imaging, adverse reactions to them are a concern. The adverse reactions have a broad clinical spectrum ranging from minor self-limiting reaction to life threatening ones. Adverse reaction to iodinated contrast agents are classified as chemotoxic and anaphylactoid reactions. The chemotoxic reactions are likely due to chemical characteristic like hyperosmolality, cation or additives. These are dose related and concentration dependent. These are manifested as cardiotoxicity, neurotoxicity and nephrotoxicity and more common in unstable and moribund patients and rarely can exacerbate myasthenia gravis or induce thyroid storm. The anaphylactoid reactions are allergic like reactions which are dose independent and non-predictable mediated by release of histamine and mediators from mast cells and basophils. Based on severity of anaphylactoid reactions, American College of Radiology (ACR) guidelines divide them in mild, moderate and severe reactions.<sup>2</sup> Mild anaphylactoid reactions are self-limited and include pruritis, urticaria, nasal congestion, rhinorrhea and conjunctivitis. Moderate anaphylactoid reactions include diffuse urticaria with stable vitals, facial edema without dyspnea and bronchospasm with no or mild hypoxia and require medication. Severe anaphylactoid reactions are life threatening as it includes edema, facial edema with dyspnea, hypotension, laryngeal edema with hypoxia and anaphylactic shock.

Incidence of overall adverse reactions is 4-12% with ionic contrast agent and 1-3% with non-ionic agents and related to hyperosmolality of agents.<sup>3</sup> Similarly, the risk of severe adverse reactions to ionic agents is about 0.2% in contrast to 0.04% to non-ionic iodinated contrast agents.<sup>4</sup> According to a study, majority of severe reactions in ionic group were allergic like while in non-ionic group were caused by cardiopulmonary decompensation and helical CT plays an important role in this changing trend.<sup>5</sup> However, reported mortality is 1-3% for both ionic and non-ionic iodinated contrast agents.<sup>6</sup>

Iodinated contrast media are generally administered through vascular route but some of these are also given through non-vascular routes and the most common are oral and per-rectal approaches. There are few reports of life threatening anaphylactoid reactions to iodinated contrast media after non-vascular administration. The primary mechanism is absorption of water soluble iodinated contrast media through mucous membrane.<sup>7</sup> However, there is no report of anaphylactoid reaction to water soluble contrast administered as enema and plausible explanation is routine dilution of media before administration.<sup>8</sup>

There is 4-6 fold increases risk of anaphylactoid reaction to patients with previous history of reaction to iodinated contrast media. Pretreatment using antihistamine and steroid (oral of methylprednisolone) has been found very effective in reducing mild and moderate reactions but relatively less effective for severe reactions and breakthrough reactions may occur. The reported incidence of breakthrough reaction to vascular LOCAs is 10%; (mild reactions 75%; 22% moderate and 3% severe) . Mild adverse reactions usually do not require intervention. Moderate and severe reactions need intervention like use of antihistamine, epinephrine (subcutaneous and intravenous), intravenous steroid, oxygen (10 liter/min) and intravenous plasma expander (normal saline or Ringer s lactate). All delayed reactions are self-limiting and do not require any specific treatment (except recipients of interleukin-2 who require steroid and antihistamine for prevention and treatment of severe delayed adverse reactions).

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