Current Radiographic Iodinated Contrast Agents

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KEYWORDS

• Iodinated contrast agents • Iodine • Triiodobenzoic acid • Contrast media • Computed tomography • Digital subtraction angiography

KEY POINTS

- The development of iodinated contrast agents has helped make significant progress in the design of safe and more effective compounds.
- Nonionic low-osmolar iodinated contrast agents are currently used in clinical practice.
- The search for an ideal iodinated contrast agent, with better imaging capabilities, lower dose requirement, and decreased toxicity is still an ongoing challenge.

INTRODUCTION

Over the last decades, the development of iodinated contrast agents has helped make significant progress in the design of safe and more effective compounds. Iodinated contrast media (CM) are most commonly administered intravenously or intra-arterially, although routes of administration include enteric, intrathecal, or direct injection, among others.[1] The first applications of CM were reported as early as the 1920s, when the first iodine-based contrast agents were used in angiographic and pyelographic applications.[2] Early iodinated CM were derived from a triiodobenzoic acid precursor and were ionic compounds of high osmolality. However, as research into the properties of CM continued, the toxicity and risk of reactions associated with ionic high osmolality CM led to the use of safer, nonionic, lower osmolality CM.[3,4]

Although different types of tissues exhibit different x-ray attenuation, the identification of the interface between normal and pathologic tissues and the delineation of soft tissue in contact with blood or other bodily fluids can be a challenge.[5] The introduction of contrast agents has allowed for more accurate imaging of anatomic boundaries by increasing the contrast between adjacent structures. The intravenous administration of CM has also enhanced our ability to study physiology, for example, organ perfusion, the integrity of the blood-brain barrier, or the excretory function via the liver or kidney, and to noninvasively assess the arterial and venous vasculature. Intra-arterial CM injection is used to deliver contrast for diagnostic catheter angiography and catheter-directed interventional procedures.[2,6] To determine the necessity for a contrast-enhanced examination, it is important to take a few considerations into account: (1) assurance that the use of contrast is both necessary and appropriate for the indication, (2) screening of the patient for any risk factors of contrast reactions, and (3) premedication of patients with risk factors and preparation for treatment of reactions should one occur.[1,2] The details of risk factors, reactions, and treatments are discussed elsewhere in this issue.

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PHYSICS, CHEMISTRY, AND SAFETY PROFILES

An effective dose of iodinated CM for computed tomography (CT) imaging is in the molar concentration range, much higher than the amount of contrast required for other imaging techniques, such as MRI (millimolar concentration range) or nuclear medicine (micromolar concentration range).[5] As a result, the search for an ideal iodinated CM, with better imaging capabilities, lower dose requirement, and decreased toxicity is still an ongoing challenge. To obtain a high level of x-ray attenuation, iodine, an element of higher atomic number (Z = 53) is introduced into the contrast agent molecule.[5] Sodium and lithium iodide were among the first iodinated contrast agents used. However, because of toxicity at the concentrations needed for imaging, these compounds were replaced by molecules with covalently bound iodine.[5] The CM molecule currently in use, triiodobenzoic acid, was first introduced in 1953.[7] The combination of a benzene ring covalently bonded to the 3 iodine atoms allows for appropriate attenuation while increasing the stability of the compound and reducing the risk of toxicity from free iodide.[6] Thus, the major characteristics that make these tri-iodinated benzene compounds safe and effective include high-contrast density, covalent bonding to benzene, and low toxicity.[5] Furthermore, the availability of the noniodinated positions 1, 3, and 5 on the benzene ring allows for modifications with hydroxyl groups or other molecules that can alter the physical, pharmacologic, and chemical properties of the compound.[5]

Iodinated compounds can be categorized by different properties, including ionization in solution (ionic vs nonionic agents), osmolality, iodine content, and viscosity.[1] In addition, iodinated CM can exist as monomers (single tri-iodinated benzene ring) or dimers (2 tri-iodinated benzene rings linked together by an organic functional group). Accordingly, iodinated compounds can be subdivided into 4 major classes: ionic monomers, ionic dimers, nonionic monomer, and nonionic dimers (**Fig. 1**).[6] These varying characteristics allow for many groups of iodinated compounds with differing properties, which in turn influence the type of agents that are used for certain clinical indications. The first-generation contrast agents were high-osmolar ionic monomers. High-osmolar contrast agents have an osmolarity up to 7 or 8 times greater than blood (≥1400 mOsm/kg) and have been associated with high risk of adverse reactions. Ionic compounds do dissociate in a solution into osmotically active cations and anions, in which the anion is the radiopaque compound.[5] The high intrinsic osmolality of these compounds potentially leads to renal

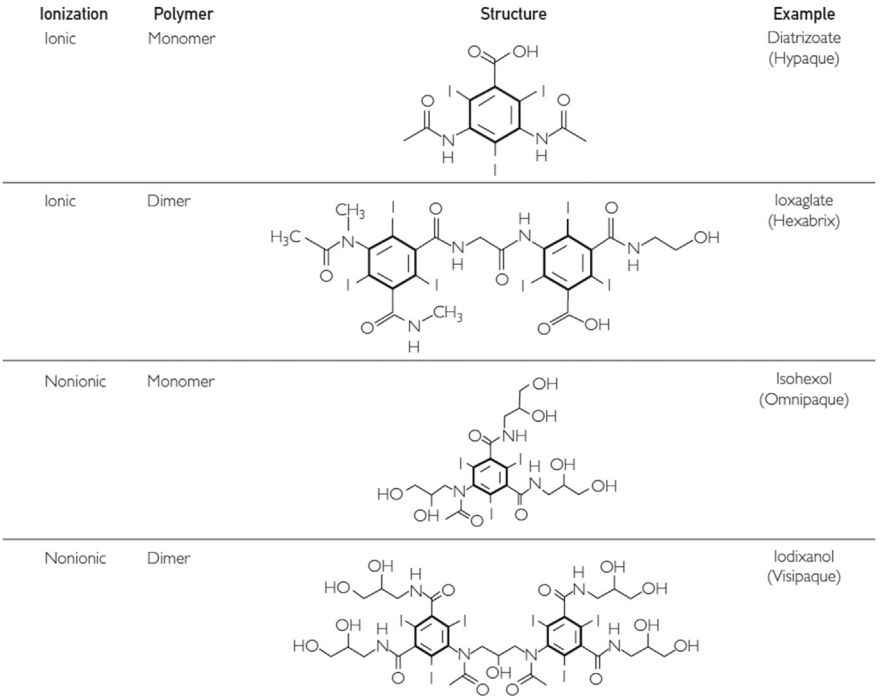

Fig. 1. Properties and molecular structure of the 4 classes of iodinate contrast agents. (*From* Pasternak JJ, Williamson EE. Clinical pharmacology, uses, and adverse reactions of iodinated contrast agents: a primer for the nonradiologist. Mayo Clin Proc 2012;87(4):393; with permission.)