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BRACHYTHERAPY ISSUES

In-stent restenosis was a vexing clinical problem prior to the release of drug-eluting stents in 2003 (see Chapter 24). Mechanical retreatment still carried high (>50%) subse- quent recurrence rates. It was then shown that intracoro- nary radiation therapy (also known as *brachytherapy* in ref- erence to the short distance between the source and the target tissue) delivered at the time of mechanical retreat- ment of the in-stent restenosis markedly reduced (by nearly 70%) the chance of subsequent recurrence (62–64). Both beta and gamma radiation were effective when

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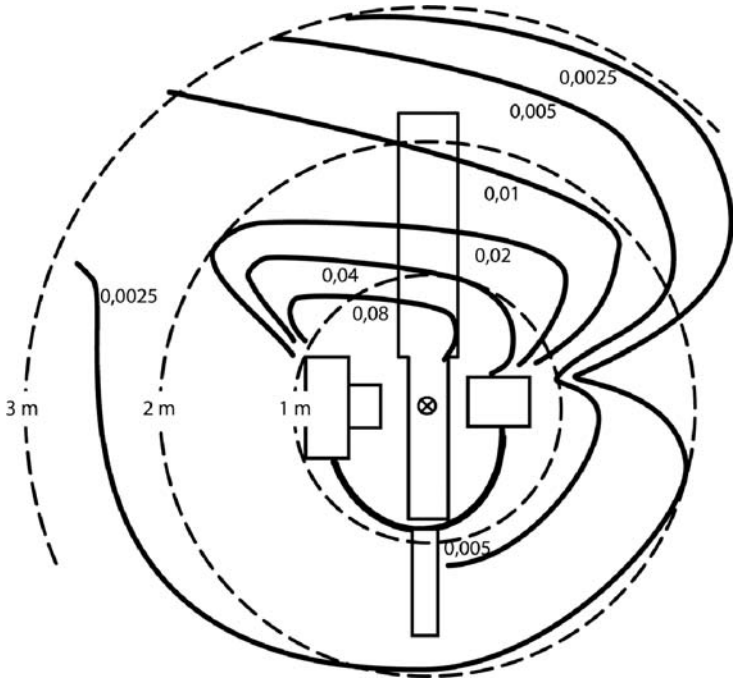

Figure 2.13 Scatter isodose curves around an interventional fluoroscope. This figure illustrates the radiation scatter levels 1 m above the floor from a full lateral beam. The asymmetry is caused by backscatter from the patient coupled with attenuation by the patient and equipment. (Figure courtesy of Philips Medical Systems.)

roughly 2,000 rads (20 Gy) was delivered to the vessel wall from radioactive seeds positioned within a catheter lying inside the treated segment. Several beta isotopic sources were used, including Sr-Y-90 and P-32, and proved to be convenient in terms of the short (3-minute) exposure times required; also, the low penetration of beta radiation made additional shielding unnecessary beyond the precaution of using a remote afterloader delivery system and avoiding operator hand contact with the catheter during source advancement. In contrast, the gamma radiation emitted from the Ir-192 source is very energetic (0.2 to 1.0 MeV, or roughly 10 times the energy of diagnostic x-ray) and would require 3 mm of lead or 2 inches of concrete for even 50% shielding (65,66). Special precautions in terms of thick portable lead shields and removal of staff from the room were required during the roughly 30-minute dwell time of the isotopic seeds in the treated arterial segment. When dealing with high-exposure sources such as these, the collaboration of both a radiation oncologist and a radiation physicist is required by NRC regulations to confirm dosing, to monitor safe handling and confirm retrieval of the source seeds, and to supervise radiation safety.

INTRAVASCULAR CONTRAST AGENTS

Shortly after publication of the classic papers by Roentgen in the 1890s, the search began for effective and nontoxic contrast agents to define vascular anatomy. Although early experimentation involved a number of heavy metals (bismuth, barium, thorium), all modern contrast agents are based exclusively on *iodine*, which by virtue of its high

atomic number and chemical versatility has proved to be an excellent agent for intravascular opacification. Inorganic iodine (sodium iodide), however, cause marked toxic reac- tions. Experiments in 1929 thus explored an organic iodide preparation (Selectan) that contained one iodine atom per benzoic acid ring. In the 1950s, a series of substi- tuted *tri-iodobenzoic acid* derivatives were developed, which contain three iodine atoms per ring. These agents differ from each other in terms of the specific side chains used in positions 1, 3, and 5 (Fig. 2.14), influencing both solubil- ity and toxicity.

Ratio-1.5 ionic compounds are substituted ionic tri- iodobenzoic acid derivatives that contain three atoms of iodine for every two ions (that is, the substituted benzoic acid ring and the accompanying cation). Included in this family of high-osmolar contrast agents are agents such as Renografin (Bracco), Hypaque (Nycomed), and Angiovist (Berlex), which are mixtures of the meglumine and sodium salts of diatrizoic acid. Functionally similar agents are based on iothalamic acid (Conray [Mallinckrodt]) or metrizoic acid (Isopaque). These agents have a sodium concentration roughly equal to blood, pH titrated between
6.0 and 7.0, and a low concentration (0.1 to 0.2 mg/mL) of calcium disodium EDTA. Higher or lower sodium con- centrations may contribute to ventricular arrhythmias dur- ing coronary injection, and calcium binding by sodium cit- rate may cause greater myocardial depression (67). To have an iodine concentration of 320 to 370 mg I/mL, as is required for left ventricular and coronary contrast injec- tion, solutions of these agents are markedly hypertonic (with an osmolality >1,500 mOsm/kg, roughly six times that of blood).

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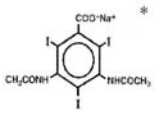
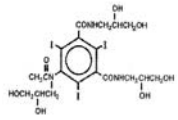
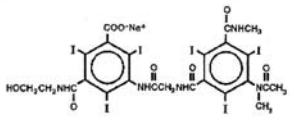
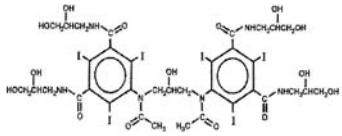
Class	Structure	Examples	Iodine	Osm	Viscosity@37⁰
High-Osmolar Ionic Ratio 1.5 (3:2)		Diatrizoate (Renografin, Hypaque, Angiovist)	370	2076	8.4
		Iothalmate (Conray)	325	1797	2.8
		Metrizoate (Isopaque)	--		
Low-Osmolar Nonionic Ratio 3 (3:1)		Iopamidol (Isovue)	370	796	9.4
		Iohexol (Omnipaque)	350	844	10.4
		Ioversol (Optiray)	350	792	9.0
		Ioxilan (Oxilan)	350	695	8.1
Low-Osmolar Ionic Dimer Ratio 3 (6:2)		Ioxaglate (Hexabrix)	320	600	7.5
Iso-Osmolar Nonlonic Dimer Ratio 6 (6:1)		Iodixanol (Visipaque)	320	290	11.8

Figure 2.14 Sample structures and properties of current available contrast agents. The traditional high-osmolar ionic contrast media (HOCM or ratio 1.5) are Na+/meglumine salts of substituted tri-iodobenzoic acid, which have three iodine atoms per anion/cation pair, with six times the osmolality of blood. Two types of low-osmolality contrast media (LOCM or ratio 3) are also shown: the true nonionic agents and the Na+/meglumine salt of an ionic dimer, which have three iodine atoms per nonionic molecule or six iodine atoms per anion/cation pair, with an osmolality two to three times that of blood. The newest class of iso-osmolar contrast medium (IOCM or ratio 6) is a nonionic dimer with six iodine atoms per molecule and an osmolarity equal to that of blood. Also included are the iodine contents (in mg I/mL), the osmolarity (Osm, in mOsm/kg-H_2O), and the viscosity at 37°C. *Mixed sodium and meglumine salt; see text for details.

In the mid-1980s, the first *ratio-3* lower-osmolality contrast materials (LOCM) were introduced. Although it is still ionic (as a mixture of meglumine and sodium salts), ioxaglate (Hexabrix [Mallinckrodt]) is a ratio-3 agent by virtue of its unique dimeric structure that includes six molecules of iodine on the dimeric ring (three atoms of iodine for every one ion). To achieve an iodine concentration of 320 mg I/mL, Hexabrix has an osmolality roughly twice that of blood and contributes to a lower incidence of undesirable side effects related to hypertonicity (68).

A more significant modification in the late 1980s, however, was the introduction of true *nonionic ratio-3* contrast agents. These low-osmolality contrast agents are water-soluble in a noncharged form, without an associated cation. Examples include iopamidol (Isovue [Bracco]), iohexol (Omnipaque [Nycomed]), metrizamide (Amipaque, [Winthrop]), ioversol (Optiray [Mallinckrodt]), and ioxilan (Oxilan [Cook]), each of which contains three atoms of iodine for every molecule (69). With calcium disodium EDTA as a stabilizer and tromethamine (1.2 to 3.6 mg/mL) as a buffer, an iodine content of 320 to 370 mg I/mL can be achieved with an osmolality of 600 to 700 mOsm/kg, between two and three times that of blood. Their viscosity (which influences ease of injection through small-lumen catheters) is roughly 6 to 10 times that of water.

More recently, a *ratio-6* nonionic dimeric compound (iodixanol, Visipaque [Nycomed]) has been released as an *iso-osmolar* contrast agent. This agent requires the addition of sodium and calcium chloride to bring its osmolarity up to that of blood (290 mOsm/kg) (70). Randomized comparisons of iodixanol to the low-osmolar contrast, ioxaglate, show that iodixanol has a significantly lower incidence of allergic reactions (<1% versus 3%) and no increase in adverse coronary events (thrombosis, vessel closure, or periprocedural myocardial infarction) (71,72). There are also data suggesting a reduction in nephrotoxicity with this agent, although the magnitude of this benefit is still unresolved (73).

As is clear from the discussion above, the low-osmolar contrast materials are definitely better tolerated by patients undergoing coronary and peripheral angiography. They produce fewer episodes of bradycardia and hypotension, precipitate less angina, and cause less nausea and sensation of heat than traditional high-osmolar contrast agents (74,75). There is also evidence that the nonionic ratio-3 and ratio-6 agents produce fewer allergic side effects (72) and may be less nephrotoxic in human studies (73,76). For all of these

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reasons, most coronary angiography is now performed with a low-osmolar contrast. Some early studies, however, sug- gested that the true nonionic agents might predispose patients to thrombotic events (77). We have not seen practi- cal clinical problems related to nonionic contrast use, which is consistent with more recent studies (71,72) that have failed to confirm any increase in deleterious thrombotic complications. The only other issue that limits the universal use of the low-osmolar and iso-osmolar agents is cost (78). These agents were once 10 times more expensive than the high-osmolar agents, and although randomized trials com- paring high- and low-osmolar agents in routine angiogra- phy have shown a clear reduction in minor side effects, they have failed to show any significant net clinical benefit in terms of serious side effects that would justify across-the- board use of a more expensive agent. Some institutions have thus confined their use to the roughly 25% of patients who have two or more of the following characteristics—age older than 65 years, left ventricular end diastolic pressure >15 mm Hg, New York heart Association functional class IV symptoms, or a history of previous contrast reaction—who would benefit most from the lower side effect profile (78). But with increasing competition among nonionic contrast agents, there has been a marked reduction in price, such that most nonionic low-osmolar agents cost only slightly more than a high-osmolar ionic agent. At such a low incremental cost, the clear reduction in minor side effects compared to the high-osmolar contrast agents may be sufficient to justify more liberal use of low-osmolar nonionic contrast.

It should be emphasized that even the best current radi- ographic contrast agents still have complications in terms of allergic reactions and kidney injury (radiocontrast nephropathy, or RCN) (79,80) (see also Chapter 3). The volume of contrast that may be used in a given procedure is thus limited, and patients with preprocedure risk factors (especially with abnormal preprocedure renal function or diabetes mellitus) (81) need aggressive preprocedure hydration, a renoprotective drug regimen (82–85), hemofil- tration, (86) as well as careful limitation of the total con- trast load. In the highest-risk patients, iodinated contrast agents may even be mixed with gadolinium-containing contrast agents designed for magnetic resonance imaging (Magnevist, Berlex), (87,88), or CO_2 angiography may be performed in the peripheral vasculature (89).