Acta Pharmaceutica Sinica B ▮▮▮▮;▮(▮):▮▮▮–▮▮▮

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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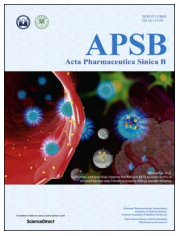

REVIEW

Radiopaque nano and polymeric materials for atherosclerosis imaging, embolization and other catheterization procedures

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Received 3 November 2017; received in revised form 18 January 2018; accepted 5 March 2018

KEY WORDS

Radiopaque contrast nanoparticles and materials;
X-ray;
CT;
Vascular diseases;
Atherosclerosis;
Plaque;
Stenosis;
Embolization;
Inferior vena cava filters

Abstract A review of radiopaque nano and polymeric materials for atherosclerosis imaging and catheterization procedures is presented in this paper. Cardiovascular diseases (CVDs) are the leading cause of death in the US with atherosclerosis as a significant contributor for mortality and morbidity. In this review paper, we discussed the physics of radiopacity and X-ray/CT, clinically used contrast agents, and the recent progress in the development of radiopaque imaging agents and devices for the diagnosis and treatment of CVDs. We focused on radiopaque imaging agents for atherosclerosis, radiopaque embolic agents and drug eluting beads, and other radiopaque medical devices related to catheterization procedures to treat CVDs. Common strategies of introducing radiopacity in the polymers, together with examples of their applications in imaging and medical devices, are also presented.

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Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

https://doi.org/10.1016/j.apsb.2018.03.002

Please cite this article as: Tian Li, et al. Radiopaque nano and polymeric materials for atherosclerosis imaging, embolization and other catheterization procedures. *Acta Pharmaceutica Sinica B* (2018), https://doi.org/10.1016/j.apsb.2018.03.002

1. Introduction

Cardiovascular disease (CVD) is responsible for a significant percentage of morbidity, mortality, and financial burden on individuals and families, particularly in developed countries like the United States[1]. Common manifestations of these diseases include vascular stenosis such as atherosclerosis, hypertension, chronic obstructive pulmonary disease, and blood-clotting disorders such as embolisms and thromboses. Though cardiovascular and blood diseases can be attributed to a variety of factors, the aging of the general population has been correlated with an increasingly prevalent diagnosis in medical practice[2,3]. The 2017 Heart Disease and Stroke Statistics Update compiled by the American Heart Association revealed that nearly 801,000 deaths were attributed to CVD, making it the leading cause of death in the United States and claiming more lives than all forms of cancer and lower respiratory diseases combined[4]. Four hundred ninety six thousand, or 61.5% of these deaths were attributed to vascular stenosis-related diseases or complications[4]. In 2010, an estimated 7,588,000 inpatient cardiovascular operations and procedures were performed in the United States and CVD also ranked highest in the number of hospital patient discharges. It should be noted that these figures only represent clinical data. It is estimated that 92.1 million US adults live with some degree of CVD. Of these, 46.7 million are estimated to be 60 years of age or older and a total of 11.5% of American adults (27.6 million) have been diagnosed with heart disease. By 2030, 43.9% of the US adult population is projected to have some form of CVD[4].

2. Radiopacity and the application in CVD imaging

Embolization procedures are often guided by ultrasound and X-ray imaging. Ultrasound is a non-invasive imaging modality which uses sound waves that have frequencies higher than what human can hear. A sound wave is generated by a transducer and partially reflected when there is a change in the acoustic impedance. The ultrasound collects the reflected waves, or echoes, and transforms them into digital images. Intravascular ultrasound has been used extensively for cardiovascular imaging and catheterization procedures[5,6]. Compared to ultrasound, X-rays have even higher frequencies, and can provide more detailed and clear images. X-ray fluoroscopy shows real-time images, facilitating interventional procedures like the guidance of catheters for embolization, and an X-ray angiogram can be used to map the vasculature along with any abnormalities like stenosis or thrombosis[7,8]. More recently, computed tomography (CT) has also been used as a noninvasive alternative to traditional X-ray techniques[9] to produce three-dimensional images and show size, shape, and composition[10,11]. However, X-ray is limited in the contrast it can provide toward differentiating between different soft tissue and healthy and pathological tissue[7]. Therefore, a contrast agent with a different radiopacity than the surrounding tissues is often used to enhance the images. We will introduce the basics of radiopacity in the following paragraphs.

2.1. Physics of X-ray and radiopacity

Although there are many different applications of X-rays, the physics behind the phenomena is largely the same. X-rays are produced by the collision and deflection of accelerated electrons with the target. The two types of resultant radiation are called Bremsstrahlung and characteristic radiation. The deflected incident electrons continue producing Bremsstrahlung and characteristic radiation until its energy is depleted[11].

In the diagnostic energy ranges, the photoelectric effect, the main form of interaction between X-ray photons and the subjects, and the Compton effect are the two processes through which photons can interact with the absorbing subject. Fig. 1 shows the relative amount of interactions by the photoelectric effect and the Compton effect[12]. The photoelectric effect occurs when a X-ray photon of higher energy than the k-/l-edge energy of the target transfers all of its energy to an inter-shell electron, causing the photon to cease to exist while a photoelectron is emitted[11,13]. The atom will then emit characteristic X-rays when a higher energy electron fills in the void left by the photoelectron.

For a CT contrast agent to be effective, images need to be taken with peak voltages higher than the k-edge of the agent, providing contrast enhancement between the surroundings and the agent itself. Hounsfield units $(HU)=1000\times(\mu-\mu_{water})/(\mu_{water}-\mu_{air})$ quantify X-ray attenuation, where μ are linear attenuation coefficients. The Hounsfield scale is standardized based on $HU_{water}=0$ and $HU_{air}=-1000$[13,14].

2.2. Clinically used radiopaque contrast agents

For vasculature and tissues to be differentiated by visual inspection, radiopaque contrast agents are administered to the areas of interest, which increases the attenuation of the targeted tissues. CT contrast agents are usually elements with large atomic numbers like iodine, barium, gold, or bismuth that have k-/l-edges of higher energies than tissue to facilitate the absorption of X-ray photons[13,15]. For CT, iodinated contrast agents are the most prevalent and FDA approved.

Iodinated contrast agents are commonly used intravenously to visualize organs and vasculature[13]. However, iodinated contrast agents also are rapidly cleared by the kidney, which means that higher doses must be given for longer CT scans[13,16]. Side effects of the iodinated agents can include contrast-induced nephropathy, nausea, vomiting, and even anaphylaxis[17,18]. Furthermore, CT contrast agents are usually on the molar concentration scale, which has researchers looking for new contrast agents with greater imaging capabilities, smaller dose requirements, and lower toxicity[14].

Small molecule iodinated contrast agents can be ionic and nonionic. Compared with nonionic contrast agents, ionic contrast agents have greater chances to interact with biological structures and have high osmolality, possibly resulting in issues like osmotic dilution and renal toxicity[19–21]. The structure of these contrast agents usually contains single or double aromatic rings[14]. Fig. 2 shows the structure of iohexol (Omnipaque), a single aromatic ring molecule. Some commercially available small molecule iodinated contrast agents are listed in Table 1.

While lanthanide-based contrast agents, specifically gadolinium chelates, are used in MRI imaging, they can also act as CT contrast agents in cardiovascular and pulmonary angiographies because of high atomic numbers, leading to better attenuation[14,22]. Gadoxetate disodium, brand name Eovist, made by Bayer Healthcare, is a contrast agent that can be used for CT imaging the liver[14,23]. However, although gadolinium compounds can be used as both MRI and CT contrast agents due to its chemical and physical properties, more research is needed to improve their efficacy as multimodal contrast agents[14]. Multimodal contrast agents based on

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