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Invited review-pharmacology across disciplines

Contrast agents in diagnostic imaging: Present and future

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ABSTRACT

Specific contrast agents have been developed for x ray examinations (mainly CT), sonography and Magnetic Resonance Imaging. Most of them are extracellular agents which create different enhancement on basis of different vascularization or on basis of different interstitial network in tissues, but some can be targeted to a particular cell line (e.g. hepatocyte).

Microbubbles can be used as carrier for therapeutic drugs which can be released in specific targets under sonographic guidance, decreasing systemic toxicity and increasing therapeutic effect.

Radiologists have to choose a particular contrast agent knowing its physical and chemical properties and the possibility of adverse reactions and balancing them with the clinical benefits of a more accurate diagnosis. As for any drug, contrast agents can cause adverse events, which are more frequent with Iodine based CA, but also with Gd based CA and even with sonographic contrast agents hypersensitivity reaction can occur.

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1. Introduction

Contrast agents enhance the differences among body tissues on diagnostic images, on basis of differences in anatomy or physiopathology. This task is accomplished by making one structure more visible than adjacent tissues. Contrast agents alter the attenuation of x-rays and the response of tissues to the applied electromagnetic or ultrasound energy by different mechanisms.

2. Computer tomography iodinated contrast agents

2.1. Introduction

Iodine-based contrast agents provide greater absorption and scattering of x-ray radiation in a target organ or blood vessel. To understand this property of iodine, it is helpful to review the underlying interactions of the x-ray photon with the iodine atom. In the energy range used in medical diagnostics, photoelectric absorption is one of the two predominant mechanisms. The x-ray photon interacting with a bound electron (generally one from the K or L shell) is entirely absorbed and the electron is ejected. The binding energy of the ejected electron is usually close to, but less than, the incident photon energy [1].

At photon energies equal to the binding energy of inner shell electrons, there is a steep increase in attenuation. This point, where the number of electrons available for interaction dramatically increases, is referred to as *absorption edge,* resulting in a dramatic rise in the attenuation value [2]. Iodine has the ideal K shell binding energy (33.2 keV), very close to the mean energy of most diagnostic X-ray beams, providing a rapid increase in attenuation compared to surrounding tissues. Iodine high atomic number also increases the probability of photoelectric absorption and decreases scattered radiation (one of the main causes of noise in the images). [3]

In computed tomography (CT) scans, contrast enhancement is directly related to the local amount of iodine and the level of x-ray energy (the tube voltage in kV) [4]. Each milligram of iodine per milliliter of blood or cubic centimeter of tissue raises the attenuation by 25Hounsfield Units (HU) [3]. Other elements of the molecule of the contrast agent do not provide radio-opacity but act as iodine carriers, increasing the solubility of the compound. Iodine-based contrast agents consist of a benzene ring to which three iodine atoms are attached (Fig. 1). Monomeric agents contain one tri-iodinated benzene ring and dimeric agents contain two tri-iodinated benzene rings. They can be classified as ionic and non-ionic agents based on their water solubility. Ionic contrast agents are water soluble as they dissociate into negative and positive ions. Non-ionic contrast agents do not dissociate and contain polar OH groups that confer them their water solubility. Due to their higher toxicity, ionic contrast agents have been rarely used in the last decades.

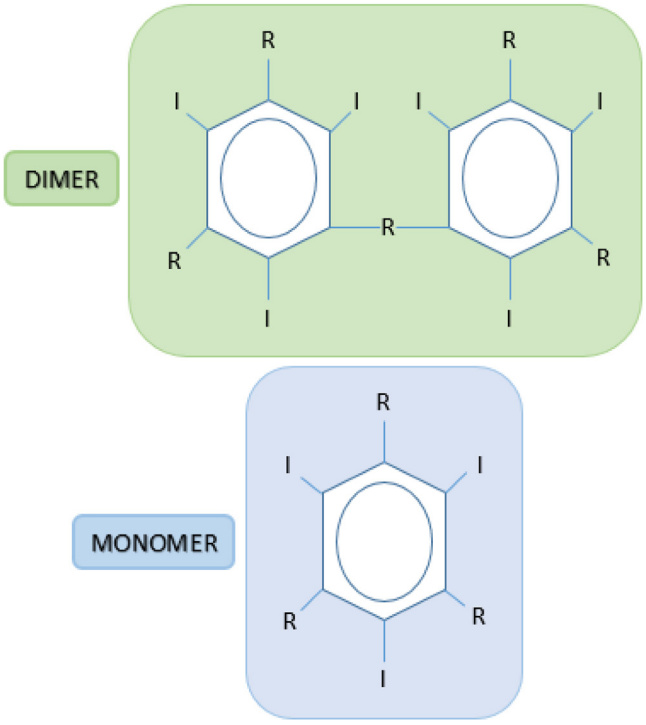

Fig. 1. Basic structure of dimeric and monomeric iodinated contrast molecules.

The average daily physiological turnover of iodine is 0.0001 g while the total iodine content in the human body (mainly in the thyroid gland) is 0.01 g. An injection of 120 mL of a contrast agent with a concentration of 370 mg of iodine/ml results in 44.4 g of iodine, delivered in less than a minute into the body. This is over 300,000 times the daily body turnover of iodine. This large quantity of iodine permeates the body with very rare evidence of severe toxicity [5].

The properties of commonly used iodine-based contrast media are summarized in Table 1.

2.2. Factors determining contrast enhancement and timing

2.2.1. Body weight

Body weight is the most relevant patient-related factor that defines the extent of parenchymal and vascular contrast enhancement. Patient weight and the degree of enhancement demonstrate a linear inverse relationship. Therefore, to maintain a constant