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CONTRAST AGENTS: TYPES AND USES

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Abstract:

Introduction: *Over the last decade, medical imaging field's advances, have been associated with increased use of contrast media (CM) notably for multi-detector computed tomography (MDCT) and magnetic resonances imaging (MRI). Similarly, expansion use of CM, using imaging guidance tools, was due to the extended spectrum of therapeutic interventional procedures in different body organs.*

Aim: *In this review, our aim was to study the different types of contrast agents and their application.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: contrast media, contrast for CT, for MRI, for X-ray, Gadolinium-based CA, Manganese-based CA, Superparamagnetic CA*

Conclusions: *X-ray examinations (mainly CT), sonography and Magnetic Resonance Imaging, these diagnostic tools had a specific contrast agent developed for them. They're mostly extracellular agents which develop different enhancement on basis of different vascularization or on basis of different interstitial network in tissues, however, few can be targeted to a specific cell line a (e.g. hepatocyte). The choice of a specific contrast agent while knowing its physical and chemical properties and the probability of side effects and reaction and balancing them with clinical benefits of a more precise diagnosis is the main task of radiologists.*

Keywords: *contrast agents, contrast media, radiographic imaging.*

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INTRODUCTION:

Over the last decade, medical imaging field's advances, have been associated with increased use of contrast media (CM) notably for multi-detector computed tomography (MDCT) and magnetic resonances imaging (MRI). Similarly, expansion use of CM, using imaging guidance tools, was due to the extended spectrum of therapeutic interventional procedures in different body organs. Capability of various medical imaging modalities were supplemented by the use of CM which are pharmaceutical formulas. Different routes can be used for administration, commonly used, is the intravenous access which is also the subject of this review. In this review, the mechanisms of various contrast media types will be discussed. Wide different contrast media types and mechanisms will be discussed as well.

METHODOLOGY:

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: contrast media, contrast for CT, for MRI, for X-ray, Gadolinium-based CA, Manganese-based CA, Superparamagnetic CA

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

Computer Tomography Agents

Greater absorption and scattering of x-ray radiation in a target organ or blood vessel is provided by iodine-based contrast agents. To be able to understand the property of iodine, it is useful to study the mechanism of interactions of the x-ray photon with the iodine atom. One of the two predominant mechanisms is photoelectric absorption which is used in medical diagnostics of energy range. Absorbed completely and ejection of electron occurs when the x-ray photon interacts with a bound electron (generally one from the K or L shell). The incident photon energy is usually more than, but close to the binding energy of the ejected electron [1].

In computed tomography (CT) scans, local amount of iodine and the level of x-ray energy (the tube voltage in kV) are directly related to the contrast enhancement. The attenuation is raised by 25Hounsfield units (HU) for each milligram of iodine per milliliter of blood or cubic centimeter of tissue. solubility of the compound is increased by the action of iodine carriers that are considered as other elements of the molecule of the contrast agent which in actuality do not provide radio-opacity. benzene ring in which three iodine atoms are attached is included in the iodine-based contrast agents. The dimeric agents contain two tri-iodinated benzene rings while Monomeric agents contain one tri-iodinated benzene ring. Based on their water solubility, they can be classified as ionic and non-ionic agents. The dissociation into negative and positive ions are the features of ionic contrast agents that are water soluble. Polar OH groups are the content of non-ionic contrast agents (do not dissociate) that grant. them their water solubility. Ionic contrast agents have been rarely used in the last decades, because of their greater toxicity [1]

Magnetic resonance imaging contrast agents

Anatomy, function, and metabolism of tissues, without exposure to ionizing radiation, are information provided by Magnetic resonance imaging (MRI) which is a non-invasive modality. large magnetic fields and radiofrequency to align and rotate the magnetic moments of protons which are contained in mobile molecules inside the human body (such as water, proteins and fat) are specific uses of MRI. The magnetic moments relax to equilibrium, once the radiofrequency pulse is turned off. Evaluation and elaboration to produce high-resolution images of normal and pathological tissues can be done, when time taken to return to the original condition occurs, also called relaxation time and differs depending on the composition and characteristics of the tissue. The proton density (ρ), the longitudinal (or spin-lattice) relaxation times T1, and the transverse (or spin-spin) relaxation times T2 are the local differences that the MRI contrast of different tissues exhibit. the sequences that emphasize T1 or T2 relaxation times are known as T1- or T2-weighted acquisitions, in the otherhand, the sequence that is mainly sensitive to ρ is called a proton-density-weighted. In some occasions, there is not enough endogenous contrast to classify tissues or detect blood flow; in these cases, the imaging capability can be improved by the usage of contrast agents (CA) [2].

MRI contrast agents' properties

Production of hyperintense (T1-weighted images) and hypointense (T2-weighted images) signals and

providing the help to evaluate tissues, perfusion, and flow-related abnormalities is done by usage of CA that shorten T1 and T2 increasing the corresponding proton relaxation rates (1/T1or r1 and 1/T2 or r2) in the area of interest. Definition of relaxivity (r) is increase in the relaxation time of the solvent (water) induced by 1 mmol L−1 of the active ion of the contrast agent is also known as the ability of a contrast agent to enhance the proton relaxation rate. Relaxivity depends on temperature and field [3].

Inner sphere and outer sphere term are the composition of relaxivity. While the outer sphere term looks into the relaxation rates of water protons diffusing local the unpaired electrons responsible for the particle's magnetization, the inner sphere term is defined as the relaxation effect originating from the closest hydrogen nuclei of water molecules interacting directly with the paramagnetic ion. For clinical agents, the effects of the outer sphere is 40% of relaxivity origin, while 60% originate from the inner sphere relaxation. R2/r1 ratio is the expression of the contrast efficiency: the higher the ratio, the more prominent the effect on T2 and vice versa on T1. T2CA usually uses superparamagnetic ions while T1 contrast agents consist mainly of paramagnetic complexes [4].

Superparamagnetic CA

polyethylene glycol, dextran and its derivatives, heparin, albumin, and liposomes are known as macromolecule materials that coat iron oxide nanoparticles, which either it or ferrites can be a content of superparamagnetic CA agents [5]. Overall particle relaxivity determines pharmacokinetics, while the dimension of the core is associated to the particle relaxivity. Alignment with the external magnetic field is intended by the magnetic moment of the cores, dephasing the transverse magnetization of water protons through an outer-sphere mechanism by the induction of local magnetic field gradients, therefore leading to shortened T2 and lower The smaller particle size is lowered by the r2/r1 ratio [4].

Classification of the nanoparticles is based on their diameter (d) in: 1) ultra-small superparamagnetic iron oxide nanoparticles (USPIONs − d less than 50 nm), 2) superparamagnetic iron oxide nanoparticles (SPIONs − d greater than 50 nm but less than 1 μm) and 3) micron-sized particles of iron oxide (MPIO − d higher than 1 μm) [6].

Metabolization of superparamagnetic particles takes place by reticuloendothelial cells. Bowel contrast, liver and spleen imaging [Ferumoxides (Feridex IV, Berlex Laboratories; and Endorem, Guerbet); Ferucarbotran (Resovist)]uses large particles [Ferumoxsil (Lumirem for Guerbet and Gastromark for Advanced Magentics], while smaller particles are used in the study of lymph nodes [Ferumoxtran-10 (AMI-227; Combidex, AMAG Pharma; Sinerem, Guerbet)] and MR angiography [Clariscan (PEG-fero; Feruglose; NC100150)] [7]. few SPIOs can additionally be used in brain and heart imaging [8]. Additionally, useful T1 agents includes USPIOs with particle size less than 10 nm. Because of economic reasons the majority of SPIONS which were accepted for medical use have been withdrawn [9].

Manganese-based CA

Manganese which is unlike Gadolinium naturally present in the body that has five unpaired electrons. Mn Paramagnetic particles can be divided in more recently developed nanometer sized materials and small molecules. Accepted clinical use were two Mn-based agents: TeslascanTM (Mn-DPDP) for liver imaging and LumenHanceTM (encapsulated Mn chloride tetrahydrate) as an oral contrast however, they're not commercially accessible anymore. To null the signal intensity of the bowel content, few natural substances which are rich in Mn (such as Pineapple) can be used as oral contrast agents [10].

Gadolinium-based CA

One type of metal from the Lanthanide family is known as Gadolinium; it is one of the most clinically used CA in MRI due to its properties and has seven unpaired electrons, few important properties include: a high magnetic moment and a long electronic spin relaxation time [11]. Today approval from EMEA (European Medicines Agency) and the US Food and Drug Administration of nine Gd-based contrast agents (GBCAs) have been conducted and are available in clinical practice. Classification of GBCAs is by the structure of ligands in cyclic or linear. Commonly, the linear is less stable than the cyclic ligand. Ligands can additionally be non-ionic, or ionic, with a charge in solution. Non-ionic compounds seem to be slightly less stable than ionic, and also, they have a lesser osmolality [12]. For safety purposes, chelates must be kinetically inert for more important in vivo use, and thermodynamically stable. Although there is a significant correlation between the chemical structure and thermodynamic in addition to kinetic stability, they're not directly related [13].

The most stable and has the longest dissociation half-life is known as Ionic macrocyclic chelates

(Gadoterate meglumine). Due to the less accessibility for chemical reactions by the "nuclear position" of Gadolinium [13]. In the commercial preparation, macrocyclic do not need ecess chelate. Lowest stability values and shortest dissociation half-life are features known for Linear non-ionic chelates (Gadoversetamide, Gadodiamide). To minimize the release of free Gadolinium they need the highest amount of excess chelate for preparation. intermediate characteristics in kinetic and thermodynamic stability are essential elements of Cyclic non-ionic (Gadobutrol, Gadoteridol) and linear ionic (Gadopentetate dimeglumine, Gadofosveset trisodium, Gadoxetate disodium, Gadobenate dimeglumine) [14].

Ultrasound contrast agents

Important characteristics of the diagnostic technique of ultrasound imaging are: high safety, low cost, and easy accessibility; it provides real-time information on morphology and vascularization of tissues with Doppler technique compared with other imaging modalities. impossibility to detect capillary network in tissues, which is useful for the differential diagnosis of lesions in many diseases, is the main limitation of this technique. Lately the introduction on the market of ultrasound contrast agents (UCAs) gave access to evaluation of tissue perfusion [15].

Properties

Unencapsulated air microbubbles were the first UCAs introduced. nevertheless, they almost completely dissolve before arrival at the pulmonary vessels and thereafter the peripheral vascular network, due to the solubility of air in blood. Development of contrast agents with proteins, lipids, and polymers shells is made to reduce the rate of gas diffusion via the surrounding tissues and to ensure thermodynamic stability leading to increase in permanence time of the gas bubbles in blood vessels. Due to the fact that Phospholipidic shells can easily be conjugated to ligands and provide good structure stability, they're used in targeting applications [16].

Due to being present in their core high molecular weight gasses (sulfur hexafluoride, perfluorocarbons) microbubbles are stable, these types of gasses do not diffuse across the shell, determining a greater persistence time in the vasculature [17]. Characteristics of the microbubble such as thickness and charge allow the production of different types of bubbles for various applications, these are several determinations that the encapsulated material exhibit. To be able to pass through the pulmonary capillaries and reach systemic capillary network, diameter of microbubbles which are normally injected intravenously as suspension must be smaller than 7 μm [18].

The low density of microbbubles and the high gas core compressibility, determine an impedance mismatch with the local structures (tissues, blood) [19].

CONCLUSION:

X-ray examinations (mainly CT), sonography and Magnetic Resonance Imaging, these diagnostic tools had a specific contrast agent developed for them. They're mostly extracellular agents which develop different enhancement on basis of different vascularization or on basis of different interstitial network in tissues, however, few can be targeted to a specific cell line a (e.g. hepatocyte). The choice of a specific contrast agent while knowing its physical and chemical properties and the probability of side effects and reaction and balancing them with clinical benefits of a more precise diagnosis is the main task of radiologists. As for any drug, adverse events can be caused by contrast agents, which are more common with iodine based CA, yet also with Gd-based CA and even with sonography contrast agents, reactions such as hypersensitivity can happen.

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