REVIEW ARTICLE

Contrasts in resonance: from linear to macrocyclic

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ABSTRACT

Introduction: the use of magnetic resonance contrast media is a necessity. In order to obtain a more effective image, the most ideal contrast should be used to minimize adverse reactions and deposition in tissues and target organs. Due to the repeated use of these contrasts in patients with oncologic follow-up of brain tumors, contrast deposits have been observed in the brain.
Objective: to study the characteristics of gadolinium-based contrast media and their use in magnetic resonance imaging.
Methods: a documentary review was carried out, theoretical methods were used for the theoretical references of the subject, the interpretation of the documentary review and the progression of the information in the articles.
Results: the toxicity of gadolinium-based contrast media depends on several factors and the occurrence of mild and severe adverse reactions with their use can be avoided.
Conclusions: for the use of gadolinium-based contrast media, the benefit/risk ratio should be assessed, this premise should coincide with the real need for an effective diagnosis and prognosis (or both). The objective is to administer the lowest possible dose, which is related to the maximum effective enhancement time.
Key words: contrast media; gadolinium; magnetic resonance spectroscopy

RESUMEN

Introducción: el empleo de medios de contraste en resonancia magnética es una necesidad, para obtener una imagen más efectiva se debe usar el contraste más ideal para minimizar las reacciones adversas y el depósito en los tejidos y en los órganos diana. Debido al uso reiterado de estos contrastes en pacientes con seguimiento oncológico de tumores cerebrales se han observado depósitos del contraste en el cerebro.
Objetivo: estudiar las características de los medios de contraste basados en el gadolinio y su uso en resonancia magnética.
Métodos: se realizó una revisión documental, se emplearon métodos teóricos para los referentes teóricos del tema, la interpretación de la revisión documental y la progresión de la información en los artículos.

Resultados: la toxicidad de los medios de contraste basados en el gadolinio depende de varios factores y la aparición de reacciones adversas leves y graves con su uso se pueden evitar.
Conclusiones: se debe valorar, para el uso de los medios de contraste basados en el gadolinio, la relación beneficio/riesgo, esta premisa debe coincidir con la necesidad real de un diagnóstico y un pronóstico (o ambos) efectivos. El objetivo es administrar la menor dosis posible, que se relacione con el tiempo de realce máximo efectivo.
Palabras clave: medios de contraste; gadolinio; espectroscopía de resonancia magnética

INTRODUCTION

The use of these contrast media in the world has been much discussed. In Cuba its handling is very careful due to its repeated use in patients with oncological follow-up of brain tumors and the real possibility of accumulation in the tissues and target organs.
A contrast agent is a medicine, that is to say, a substance that when administered to the organism is capable of preventing, curing, palliating or diagnosing (as in this case) a disease. This type of substance has the characteristic of reaching some tissues and not others, in one concentration or another and at one time or another. In this way the signal emitted by the patient is modified and the diagnosis is improved. The basis of contrasts in magnetic resonance imaging (MRI) is the intrinsic magnetic susceptibility of the compound that includes the contrast, that is, the availability of that substance to be magnetized (magnetized) in an external magnetic field. It is contrasted in MRI in order to increase diagnostic imaging efficiency through better tissue definition, to increase the differences between normal and pathological tissue and to provide functional information, determined by the degree of actual enhancement as a function of the time elapsed since the contrast administration.[1]
The ideal contrast should meet all the requirements that characterize the action of a drug to the highest degree. It should have an activity of maximum influence on the parameters responsible for the MR signal (T1 and T2 relaxation time) and zero toxicity. Pharmacokinetics characterized by easy administration (preferably oral), selective distribution, rapid and complete elimination, high stability and cost-effective efficiency are indispensable.[1]
Gadolinium-based contrast agents (GBCA) are the most recognized contrast media on the market. This chemical element, with atomic number 64 in the periodic table, belongs to the rare earth group and is composed of eight isotopes. It is named after the Swedish scientist J. Gadolin. Its chemical structure determines its magnetic susceptibility, it is paramagnetic, which allows a quality signal. By its physical and chemical characteristics it can be ionic, nonionic, isoosmolar or hyposmolar. As it is a toxic metal, its classification, according to the morphology of the molecule of the chelating substance that holds it, can be of linear or macrocyclic morphology and limits its toxicity in the organism.[1,2]
Due to the repeated use of these contrasts in patients with oncologic follow-up of brain tumors, contrast deposits have been observed in the brain.

METHODS

A documentary review was carried out in order to study Gadolinium contrast media and their use in magnetic resonance imaging. Its pharmacokinetic characteristics, the adverse reactions described in the literature and the precautions to be taken into account to avoid their occurrence were identified, due to the fact that contrast media became not so safe drugs in the last decades. Google Scholar was used as a search engine and the keywords used were: contrast media, gadolinium, magnetic resonance spectroscopy.

DEVELOPMENT

A contrast medium must possess adequate magnetic susceptibility to allow an accurate diagnosis, just as a gadolinium compound must possess pharmacokinetic characteristics that determine a lower incidence of adverse reactions in patients.

Gadolinium-based contrast agents (GBCA), by administration, have the ability to be bound to the chelating agent, which forms chelates and which, through chemical antagonism, reacts and binds to the cation and forms a more stable cyclic compound. Chelating agents are organic compounds that bind heavy metals. The chelates formed from the binding are composed of a chelating agent and a MCBGd, pharmacokinetic properties that facilitate their administration, metabolism and elimination. In addition, they significantly decrease their toxicity, biological interactions and deposition in tissues.[3,4,5]

The chelates formed have a very small toxicity, being poorly dissociable complexes and large molecules they are water soluble and do not bind to albumin, are not metabolized and have renal excretion; their distribution is extracellular.[1,5,6] Theoretically, the interaction of drugs such as chelating agents with intracellular and extracellular elements, which are not receptors, is described; they are called drug target elements, in which the chelating agents bind cations.[5,6] This binding to target elements sometimes determines the formation of a reservoir in the tissues with the potential to cause local adverse effects.[5]

This interaction and fixation of cations determines accumulation of the contrast medium, so the toxicity of gadolinium compounds will depend directly on the stability of the chelate, which is defined by the value of the thermodynamic constant of dissociation of the preparation with respect to time.[1,6] This dissociation occurs spontaneously and obeys the laws of thermodynamics and the interaction of matter; however, its half-life can be modified by factors such as the presence of enzymes, temperature and pH. In practical terms, the greater the stability, the less likely a MCBGd is to release toxic Gd^{3+} into the organism.[3]

Consideration should be given to the use of compounds with extracellular distribution and avoid those with specific target tissue distribution. Among the most commonly used contrast media with this characteristic are gadopentate dimeglumine (Gd-DTPA) -1983, magnevist-, which is linear and ionic; gadodiamine (Gd-DTPA-BMA) -1983-, which is linear and nonionic;

meglumine gadoterate (Gd-DOTA) (1988), which is cyclic and nonionic; and gadobutrol (Gd-BT-DO3A) -gadovist-, which is macrocyclic and nonionic.[1,3,4]
When assessing the safety of a contrast medium from the pharmacokinetic point of view, the osmolarity of the preparation must be taken into account, which will influence the occurrence of adverse effects, especially nausea and vomiting, in a rapid injection.[1,6] When administered intravenously a hyperosmolar substance causes an elevation of plasma osmolarity with intracellular dehydration and an alteration of blood metabolites, leading to vascular pain, endothelial injury and vasodilatation with hypotension and hypovolemia due to bradycardia (or both).[1,2]
Ideally, the osmolarity of the preparation should be as close as possible to plasma osmolarity (isoosmolar), which is 300 mOsm; viscosity should be low to avoid toxicity. The pharmacological characteristics of Gadolinium-Based Contrast Agents (GBCA) are similar; the main difference is in their structure and ionic charge.[1] Differences in electrical charge can alter contrast uptake in tissues with negatively charged components, such as mucopolysaccharides.[6,7,8,9,10,11] The stability of gadolinium chelates is very high and macrocyclic compounds bind the gadolinium ion more strongly than those with a linear structure. Ionicity improves the stability of the molecule. Non-ionic agents have a lower osmolarity and are less viscous. Macrocyclic and ionic MCBGd are the most stable and have the least risk of dissociating and releasing the toxic gadolinium ion.[1,3,6]
The GBCA were classified as very safe in past decades, although they can produce adverse reactions with a prevalence between 0.17% and 2.4%.[1,6] The most frequent side effects were very mild, mainly nausea-vomiting, but a sensation of heat or cold (injection rate), pain at the injection site (injection rate), dizziness, headache, nausea (injection rate), dysgeusia or metallic taste and urticaria (rare, may be warning of severe reaction) are also assessed; they are seen more in atopic, asthmatic patients or with a rapid infusion rate. They can also produce convulsions (very rare, be very careful in epileptic patients) and anaphylactic reaction (very rare, can be severe/fatal).[1,3] In the hospital setting, nephrogenic systemic fibrosis (NSF) has begun to be observed in the last twenty years and with some frequency as a side effect to be taken into account; it was in 2006 when its association with the administration of gadolinium contrast in patients with renal failure was described. It presented as a systemic inflammatory disease of the connective tissue in patients with renal damage. Renal damage can determine difficulties in renal elimination by increasing the elimination time, which depends on the rate of dissociation of contrasts as a function of time, the longer the elimination time the greater the probability of separation of Gd^{3+} from its chelating agent. It has been seen in patients with intact renal function, in whom it appears after the fifth dose.[3]
In 2009 the Spanish drug agency classified these contrast media according to the data published up to that time and according to the risk associated with NSF and identified gadoteridol (prohanse), meglumine gadoterate (dotarem) and gadobutrol (gadovist) as low-risk contrasts. It established guidelines for the administration of high-risk contrast agents in patients with severe renal failure (glomerular filtration rate greater than 30 ml/min/1.73m^2), with hepatic or renal transplantation (or both) and in children under one year of

age, and indicated not to exceed a dose of 0.1 mmol/kg in patients with a glomerular filtration rate of less than 30 ml/min/1.73m^2. The choice of the appropriate contrast should be considered through a benefit/risk assessment in patients with a glomerular filtration rate lower than 30 ml/min/1.73m^2 and in patients with normal renal function the risk of allergic reaction should be further considered. A decrease in NSF was evidenced in 2008, even in patients with renal damage undergoing dialysis; this occurred due to the follow-up of the recommendations.[1,2,4]

In the last decade, and fundamentally in the last three years, allergic reactions to these contrasts have appeared published, with a prevalence of 0.04 and up to 0.07%,[1] so it should be taken into account that the personnel who administer the contrast should be trained in the early appearance and immediate management of adverse reactions.[2,4,7]

It was first described, in 2013, by Kanda et al, the association between the use of GBCA and the progressive increase in signal intensity of the dentate nucleus (DN) and globus pallidus (GP) in T1-weighted MR images without contrast medium and, when compared with the number of previous doses, they found a statistically significant correlation; according to the authors this indicates a progressive deposition of Gd in the neural tissue secondary to multiple doses of GBCA and not to the treatment used or to the natural history of the disease. This theory was tested in a study by Quattrocchi et al. in which follow-up MRI was evaluated in patients with meningiomas under conservative management and with observation protocols without any therapeutic intervention; they found the same progressive changes of DN and GP.[3]

Mc Donals et al. in 2015 published a study in which they used inductively coupled plasma mass spectrometry (ICP-MS) to quantify Gd content in brain tissue samples from patients with normal renal function. The brain tissue samples were obtained from autopsies of 13 patients undergoing at least four MRI scans with MCBGd in the last 14 years and quantifiable levels were found in the capillary endothelium and nerve tissue interstitium, primarily in the DN. In addition, they made a comparison with samples obtained from 10 patients who were not exposed, who did not present images of Gd deposits.[3] In the central nervous system (CNS) the distribution of drugs from the blood to the CNS is through the cells of the capillary endothelium with very tight and continuous junctions, the penetration of the drug depends on transcellular transport. In the choroid plexus there is a barrier of blood and cerebrospinal fluid (CSF) in which epithelial cells are bound by tight junctions.[5,7,9] Theoretically, the nonionic and free lipid-soluble forms of the drug are a determining factor in its uptake by the brain. The more lipophilic a drug is, the easier it crosses the blood-brain barrier (BBB).[5,8]

The deposition of Gd, with an intact BBB, is due to two fundamental mechanisms: transmetallation, which is the exchange of a metal such as Gd^{3+} from an MCBGd for another ion of similar structural characteristics such as Zn^{2+}, Mg^{2+}, Ca^{2+} and Fe^{3+} of a macromolecule involved in certain metabolic pathways and the diffusion of Gd3+ as a free ion after dissociating from the chelating agent of an unstable MCBGd.[3,9]

The deposition of this metal in the DN and GPs is proportional to the number of gadolinium doses received and is more marked with the use of linear

nonionic MCBGd due to the weakness of the chelating agent molecule that allows these to be released. The U.S. Food and Drug Administration (FDA), in a May 2017 statement, cautions that GBCA deposit in patients' bodies, including the brain, for months to years, acknowledges that the deposit has not been directly linked to adverse health effects in patients with normal renal function, and posits that the benefit of approved GBCA outweighs any potential risks.[10]

In July 2017 the European Medicines Agency (EMA), through the Committee for Medicinal Products for Human Use (CHMP) and the Spanish Agency for Medicines and Health Products (AEPS, Agencia Española de Medicamentos y Productos Sanitarios), declared that as a product of gadolinium retention in brain tissue, due to the administration of intravenous linear compounds, its use in the European Union should be suspended. To date, there is no scientific evidence of brain damage and the long-term effects are unknown. Only gadoxetic acid and gadobenic acid were authorized for liver studies and gadopentin for intra-articular studies. It recommends that contrasts should only be used when essential diagnostic information cannot be obtained with non-contrast images and to use the lowest possible dose to obtain the maximum enhancement time necessary for a good diagnosis.[4,12] The AEPS, based on the recommendations of the European Committee for Risk Assessment in Pharmacovigilance, established that the relationship between clinical benefits does not outweigh the possible risks derived from the use of contrasts of linear structure that must be taken into account.[12,13]

Due to the repeated use of these contrasts in patients with oncologic follow-up of brain tumors, a more ideal contrast should be used in which the gadovist proposal can be analyzed due to its low risk. Gadobutrol (Gd-BT-DO3A) (gadovist) is a very stable macrocyclic contrast, it is non-ionic and has a high T1 relaxivity, which guarantees a higher enhancement and better visualization of the lesions, with less doses.[1,11,13,14,15,16]

It is necessary to take into account the need to perform the study, whether or not to use contrasts and if their use is going to change the diagnosis or prognosis (or both), establish the adequate pulse sequences and carefully evaluate the contrast dose in relation to the maximum contrast enhancement time.

CONCLUSIONS

For the use of gadolinium-based contrast media, the benefit/risk ratio must be assessed, this premise must coincide with the real need for an effective diagnosis and prognosis (or both) and administer the lowest possible dose, which is related to the maximum effective enhancement time, that is the objective to be achieved.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.