J of Nuclear Medicine Technology, first published online February 15, 2019 as doi:10.2967/jnmt.118.220012

PHARMACOLOGY PART 5: CT AND MRI CONTRAST.

Geoffrey M Currie

Faculty of Science, Charles Sturt University, Wagga Wagga, Australia.
Regis University, Boston, USA.

Correspondence:
Geoff Currie
Faculty of Science
Locked Bag 588
Charles Sturt University
Wagga Wagga 2678
Australia
Telephone: 02 69332822
Facsimile: 02 69332588
Email: gcurrie@csu.edu.au

Foot line: Pharmacology of CT and MRI contrast

ABSTRACT

Pharmacology principles provide key understanding that underpins the clinical and research roles of nuclear medicine practitioners. The scope of practice of the nuclear medicine technologist demands knowledge and understanding of indications, contraindications, warnings, precautions, proper use, drug interactions, and adverse reactions for each medication to be used. This article is the sixth in a series of articles that aims to enhance the understanding of pharmacological principles relevant to nuclear medicine. This article will build on the introductory concepts, terminology and principles of pharmacology explored in the first two articles in the series. Specifically, this article will focus on the pharmacological principles and adverse reactions associated with iodinated and gadolinium contrast employed in computed tomography (CT) and magnetic resonance imaging (MRI) respectively. The next article in the series will address the pharmacology related to the emergency trolley (crash cart).

INTRODUCTION

In imaging, a contrast agent is any agent that is administered to the patient in order to improve the visualization of an organ, tissue or pathology. Generally, contrast agents are positive (increases opacity) but some negative contrast agents (decrease opacity) exist (eg. air or gases). In the context of this article, the positive contrast agents associated with iodine and gadolinium will be discussed, Specifically, iodinated contrast agents will be outlined with reference to computed tomography (CT) and gadolinium for magnetic resonance imaging (MRI) as appropriate for the target readership. It should, however, be noted that both gadolinium and iodinated contrast agents are used outside of MRI and CT respectively.

While contrast agents have become safer and better tolerated in recent decades, adverse reactions still occur to varying degrees. Consequently, it is essential that those administering contrast or monitoring patients post contrast administration are familiar with the pharmacology and adverse reactions associated with those contrast agents. Foundations of pharmacology and pharmacokinetics outlined in previous articles in this series, including specific medication profiles, will be considered assumed knowledge (*1-5*). This insight and understanding will facilitate early detection of adverse reactions and inform a response with the most appropriate management.

CT CONTRAST

Introduction to CT Contrast

Ideally, a contrast agent for CT would be able to provide opacification of blood vessels, organs and tissues without altering physiology or producing toxicity (*6*). The iodine molecule can absorb x-rays to provide contrast and has been the basis of intravenous (IV) contrast since 1929 (*6*). The development of organic iodinated compounds emerged because the inorganic sodium iodide was too toxic for regular or routine use (*6*). Today CT contrast is based on the structure that emerged in the 1950s; tri-iodinated derivatives of benzoic acid that were ionic and high osmolality (*6-9*). Current agents are either monomers or dimers (one or two benzene rings), ionic or nonionic, high or low osmolality or isotonic, and vary in viscosity (*7-10*). It is important to note that almost all current CT contrast agents are iodine based. The emergence of non-ionic CT contrast created the misnomer that they were non-iodinated; non-ionic does not mean no iodine. More than 50 million CT studies are performed in the USA each year of which, an estimated 50% (25 million) include IV contrast (*11*). Worldwide, there are an estimated 75 million IV CT contrast doses annually (*10*).

Properties of CT Contrast

There are a number of key properties of iodinated contrast agents that influence their behaviour, efficiency and their adverse reaction risk / profile. There is an interplay between these properties that optimise the degree of radio-opacification and its tolerability / toxicity including (table 1):

- Iodine concentration is the amount of iodine (mg) per unit volume (mL) of the contrast solution administered.
- Osmolality is a measure of the number of active particles when dissolved in 1kg of water expressed as milliosmoles/kilogram (mOsm/kg) (*12,13*).
- Viscosity is internal or flow friction, resistance or thickness of the fluid (*8,12*)
- Ionicity is the tendency for the contrast agent to separate into charged species (ions) when dissolved in solution.

- Oligomerization refers to the chemical structure being either a monomer or dimer.
- The dose delivered to the patient can vary in both relative (mg/kg) and absolute (mg I) terms but also the time course over which it is administered.

Iodine concentration amongst iodinated CT contrast agents ranges from 11-46% with higher iodine concentrations providing both better radio-opacification but higher risk of adverse reaction (*12*). Today, most current generation CT contrast agents are non-ionic, however, they often vary significantly in terms of iodine content (*7,12*). The dimer configuration is designed to reduce the risk of adverse reaction / toxicity without compromising radio-opacification. Typically, the iodine concentration of common iodinated contrast agents is in the order of 300 mg/mL, however, range from 200 mg/mL to 400 mg/mL (table 1). Indeed, the same contrast agent maybe be marketed and branded with varying iodine concentrations (eg. Omnipaque 240, Omnipaque 300, and Omnipaque 370). Increasing iodine concentration increases viscosity.

Osmolality introduces the concept of tonicity; hypertonic or isotonic for example. Tonicity relates to the impact of the osmolality of a solution on the surrounding cells (*12*). Isotonic solutions (like most radiopharmaceuticals) have an osmolality that equals blood (290 mOsm/kg water) and thus has no impact on surrounding cells (*12*). Hypertonic solutions have a higher osmolality than blood and this results in water being drawn out of blood cells (*12*). Iodinated contrast agents in CT can have an osmolality seven times that of blood. Hypotonic solutions have a lower osmolality than blood and this results in water being taken into blood cells (*12*). Iodinated contrast agents are classified as high osmolality contrast media (HOCM), low osmolality contrast media (LOCM) or iso-osmolar contrast media (IOCM) (table 1) (*12*). There are no hypotonic iodinated contrast agents. Both HOCM and LOCM are hypertonic, just to varying degrees. Older iodinated contrast agents are typically HOCM (1300-2140 mOsm/kg water) while newer

contrast agents developed from the 1980s are typically LOCM (600-850 mOsm/kg water). As outlined below, osmolality contributes to the incidence of non-anaphylactoid adverse reactions mediated by endothelial damage, movement of fluid amongst compartments, and cell deformation. IOCM iodinated contrast agents are a more recent development with osmolality that equals that of blood. Given the aim of iodinated CT contrast agents is to have sufficient iodine concentration for radio-opacification, the ratio of iodine atoms to particles in solution is important; HOCM is 0.5, LOCM is 3.0 and IOCM is 6.0. Adverse effects attributable to osmolality include pain, flushing, nausea, vomiting, and dehydration (*12*). Contrast osmolality higher than blood (HOCM and LOCM) results in movement of water from interstitial spaces into the vascular compartment which causes increased blood viscosity, endothelial damage, hypervolemia, vasodilation, edema with neurotoxicity, decreased myocardial contractility and toxicity (*6*).

The viscosity of iodinated CT contrast agents is determined by the flow friction, resistance or thickness of the contrast media (*8,12*). Iodinated contrast is significantly more viscous than radiopharmaceuticals and this impacts on IV injectability, flow rate and gauge of canula required. Viscosity can be reduced by injecting the contrast at body temperature (37ºC) rather than room temperature and it is worth noting that viscosity of iodinated contrast media at 20ºC is approximately twice that of the same agent at 37ºC (*12*). Viscosity is influenced by the molecular structure and composition of the contrast agent with inclusion of sodium decreasing viscosity but increasing endothelial irritation compared to meglumine, LOCM has higher viscosity over HOCM, and viscosity increases with iodine content (table 1) (*12*). Viscosity plays an important role in renal tolerance, contributing significantly to the risk of contrast induced nephrotoxicity (*7*). High viscosity IV iodinated contrast agents require longer infusion times (*8*) while low viscosity allows the use of a rapid bolus (*12*); a key factor in optimizing the contrast agent for imaging protocol. High viscosity IV contrast agents also exert an influence on the local circulation (*8*). Water is used as the reference standard

for viscosity at 1 centipoises (cps), plasma is then 1.5-2 cps, and iodinated CT contrast agents range from 2.0 cps for low iodine concentration, non-ionic, monomer-based contrast up to 11.4 cps (*12*).

Contrast agents used IV in CT are tri-iodinated derivatives of benzoic acid (figure 1) (*6-9*). A monomer is simple molecule or base unit that can undergo polymerization. In the case of iodinated contrast agents, it is a 2,4,6 tri-iodinated benzene ring (figure 1). A dimer is two bonded monomer units following polymerization to form a two-unit oligomer. Monomers have higher osmolality than dimers with dimers typically being LOCM or IOCM (table 1) (*7*). Covalently bonded iodine atom associated with CT contrast agents are within the range of x-ray wavelengths so can produce attenuation (*10*). This is enhanced by the close proximity of the tri-iodinated configuration; enhancing attenuation properties (*10*). Importantly, the benzine ring structure reduces the risk of toxicity (*10*).

Ionic iodinated CT contrast agents dissociate into ion pairs while non-ionic do not (figure 1) (*13*). Non-ionic does not mean non-iodinated, nor does it mean LOCM even though most non-ionic contrast is LOCM. Fully saturated tri-iodinated benzoic acid derivative monomer CT contrast agents dissociate into ions in solution; the anion containing the iodine atoms and the cation containing sodium and/or meglumine (*6,8,9,12,13*). These are typically hypertonic (osmolality five times that of blood) and alter the plasma tonicity (*6*). Consequently, adverse reactions are common (*6,12*). The dimer form (two tri-iodinated benzoic acid rings) allows high iodine content but low osmolality because a single cation is still all that is required (*6,8,9,12*). Only the anion is radio-opaque because it carries the iodine atoms but the cation is needed for the solution to be formed (*1*).

Non-ionic monomer CT contrast agents have a longer side chain than ionic monomers (figure 1) and this increases the molecular weight, decreases the osmolality but does not change the iodine concentration (*6,8,12*). The non-ionic dimer structures tend to be isotonic (*6*). Low osmolality agents are less toxic and

have fewer adverse reactions (*6*). The four major classifications of iodinated CT contrast agents include ionic monomer, ionic dimer, non-ionic monomer, and non-ionic dimer (figure 1) (*8-10*).

Individual doses for patents should be tailored in consideration of the properties outlined above and (*14*):

- iodine concentration,
- volume of dose,
- patient height, weight, age, and gender,
- venous accessibility,
- renal function,
- pharmacokinetic model (discussed below),
- injection rate,
- target organ,
- target enhancement,
- CT scanner and imaging protocol.

Mechanism of Action

While a discussion of the physical principles of x-ray production in CT is beyond the scope of this article, it is important to briefly revise key principles that contribute to the effectiveness of iodinated CT contrast media. An incident x-ray can undergo photoelectric absorption following interaction with an inner shell electron of an atom in the attenuating medium when the x-ray energy is fractionally in excess of the binding energy of the electron (*15*). The subsequent ejection and replacement of the electron from an outer shell results in production of a characteristic x-ray (*15*).

The photoelectric interaction does not occur when the incident x-ray energy is less than the binding energy of the electron (*15*). If, however, the incident energy is equal to the binding energy, the photelectric effect becomes possible and a disproportionate increase in attenuation occurs (*15*). Beyond the binding energy

equivalent for the incident x-ray, the probability of photoelectric interaction decreases (*15*). The K-edge refers to the abrupt increase in attenuation when the energy of the incident x-ray approximates the K binding energy (figure 2) (*15*).

The human body is largely comprised of low atomic mass elements with corresponding low K shell binding energies (*15*). Higher atomic masses associated with, amongst many elements, iodine, gadolinium and lead have high K shell binding energies producing characteristic x-rays with relatively high energies (*15*). This principle allows higher atomic mass elements to be utilized for contrast media or detector material (*15*).

Since the photoelectric effect has a higher probability of occurring between low energy x-rays and high atomic mass elements, it provides excellent properties as a CT contrast agent. Iodine, for example, has approximately 350 times higher attenuation than soft tissue at the same energy (*15*). This can be exploited in CT contrast imaging. The K shell binding energy for x-rays is 33.2 keV for iodine but rather than attempting imaging with a monochromatic beam at that energy, kVp (60-80) can be optimized to produce a good proportion of x-rays in the 33-40 keV range. In this energy range, attenuation is greater for iodine than it is for lead (figure 2) (*15*).

Pharmacokinetics

Iodinated CT contrast agents are best described using a two-compartment model (figure 3). Iodinated contrast agents demonstrate rapid peak plasma concentration at 2 minutes post IV (*6-8*). A biphasic plasma profile represents rapid diffusion of the contrast from the plasma compartment into the interstitial compartment and then slow urinary clearance (*6,8*). The peak plasma concentration at 2 minutes post IV shortens to 1 minute with higher doses (*7*). Only 1-3% of iodinated contrast agents are plasma protein binding (*8*). As contrast diffuses into the extravascular space, water is drawn from extravascular space into the intravascular space due to osmolality. Tight junctions prevent

movement of contrast into extravascular spaces in the brain, testes and neural tissues.

The biphasic half lives vary from one agent to the next but tend to be approximately 7 minutes (range of 2-30 min) and 1.6 hours (range 1-2 hours) but these half lives universally increase with increasing contrast dose (*6-8*). In renal dysfunction, elimination half life can increase to 40 hours or longer (*8*). The IV CT contrast agents do not undergo metabolism and are almost exclusively excreted by glomeruli filtration in urine unchanged in a similar fashion to inulin (*6,8*). The proportion of the contrast dose in urine is variable between agents but in normal patients is in the range of 12% at 10 minutes, 50% at 1 hour, 83% at 3 hours and virtually 100% at 24 hours (*6-8*). Contrast agents may have individual and collective maximum volumes requiring awareness of previous procedures and specifications of agent in use.

Calcium or magnesium has been added to newer contrast agents to reduce toxicity (*12*). All ionic contrast media bind invivo to calcium and magnesium (*12*). If given orally, CT contrast agents are absorbed from intestine, glucuro-conjugated, strongly plasma protein bound and then rapidly concentrated and eliminated in the biliary system (*6*).

Adverse Reactions

Adverse effects are common and classified in several overlapping ways; by type of reaction, by severity of reaction or by mechanism of reaction (figure 4). Based on a classification of the type of adverse reaction, contrast agents in CT can produce general reactions or organ specific reactions (*11,16*). Organ specific reactions include toxicity associated with renal, cardiovascular, pulmonary or neurological systems (*11*). General reactions can be acute or delayed with the latter tending to be skin reactions (*11*). Acute general reactions can be mild self-limiting in nature or moderate to severe requiring intervention (*10-12,16*). If appropriate, adverse reactions should be reported to the regulatory authority.

The incidence of adverse reactions to IV iodinated contrast is higher for ionic than non-ionic contrast (table 2) (*10-12,16*). The most common adverse reactions to CT iodinated contrast are hives (52.5%) and nausea (17.6%) (*13*). Prior adverse reactions to CT contrast are a significant predictor of a subsequent reaction. There is a prevalence of 17-35% for adverse reactions to ionic contrast in those with previous reactions and 5% for non-ionic contrast (*11*). Other predictors or risk factors for developing an adverse reaction to iodinated IV contrast include a history of asthma, history of allergies, heart disease, dehydration, sickle cell disease, polycythemia, myeloma and underlying renal disease (*11-13,16*). Risks of adverse reactions are also higher in infants or the elderly, during periods of anxiety and with the use of medications like beta blockers, non-steroidal anti-inflammatories (NSAIDs) and interleukin-2 (*11,13,16*).

Fatal adverse reactions can occur but rarely (1 in 170000 cases) (*10-12*) but with 25 million CT contrast studies annually in the USA, that equates to 150 deaths in the USA annually. The risk of a fatal adverse effect increases for women, the elderly, Anglo-Saxon and those with comorbidity (*11*). This has been referred to as the four W's; women, wrinkled, white and weakened (*11*). Generally, the cause of death in fatal CT contrast reactions are associated with renal failure (58%), anaphylaxis / allergy (19%), cardiopulmonary arrest (10%), respiratory failure (8%) and stroke / cerebral hypoxia (4%) (*11*).

Delayed general adverse reactions occur 1 hour to 1 week after the IV contrast injection (*10-12*). Delayed reactions tend to be skin reactions and more likely for dimeric isomolar agents or in young adults, women and those with a history of allergy (*10,11*).

Describing adverse reactions to contrast by the mechanism creates three classifications; anaphylactoid, chemotoxic (organ specific) and vasovagal (*12,17*). Anaphylactic reactions are associated with an allergen/IgE mediated release of chemical mediators like histamine from mast cells (*12,17*). Anaphylactoid

reactions like those of iodinated contrast agents are similar to anaphylactic reactions in terms of activation of mast cells but they are not initiated by the allergen/IgE complex (*12,13,17*). This is important to understand because it means that an anaphylactoid CT contrast reaction can occur with the first administration (no sensitization), reaction severity is not dose related (test doses are unhelpful), and a previous history of contrast reaction increases the risk of a subsequent reaction but it does not mean it will occur (*17*). Non-anaphylactoid reactions are dose dependent (*17*). Nonetheless, patients with asthma, food or medication allergies, mastocytosis and prior contrast reactions are at highest risk of an anaphylactoid reaction (*12,13*).

Chemotoxic adverse reactions are associated with the ionicity, iodine concentration, viscosity, osmolality, injection rate and dose of the contrast agent; all contributing to alterations to homeostasis (*12,17*). Contrast induced nephrotoxicity suffers a lack of uniform definition around the degree of resulting renal dysfunction but incidence does vary with baseline renal function status (*10-12*). There is a 1-3% risk of developing nephrotoxicity in patients with normal baseline renal function, 12-27% in those with pre-existing renal dysfunction and 50% on those with diabetic nephropathy (*11,12*). Preventative strategies include 6-12 hours of pre-hydration followed by 4-12 hours of post-hydration, and the use of non-ionic contrast using the minimum dose (*11*). 600mg twice daily for 48 hours prior to the study of N-Acetylcysteine has also been used prophylactically (*10,11*). Sodium bicarbonate infusion starting 1 hour before contrast administration and continued until 6 hours after contrast administration has also been used (*11*).

Screening patients based on health history and renal function is perhaps the best strategy for minimizing acute contrast induced nephrotoxicity. Indeed, estimated glomeruli filtration rate (GFR) from serum creatinine levels has been used effectively to predict risk. A GFR greater than 60 ml/min/1.73m^2 is associated with negligible risk of contrast induced nephrotoxicity (*11*). Conversely, a GFR of

30-60 ml/min/1.73m^2 is associated with a moderate risk of contrast induced nephrotoxicity and a GFR of less than 30 ml/min/1.73m^2 is associated with a high risk (relatively contraindicated) of contrast induced nephrotoxicity (*11*). Serum creatinine levels should be assessed prior to CT contrast administration in patients with a history of renal disease, a family history of renal disease, diabetes, myeloma, collagen vascular disease or if they are on medications like metformin, NSAIDs and aminoglycosides (*11,12*). Creatinine assessment is also recommended in patients with a history of renal transplant, renal tumor or renal surgery, in patients with end stage liver disease, and in patients with severe congestive heart failure (*12*).

The molecular weight of iodinated contrast agents allows ready filtration in the glomeruli. The virtual 100% elimination of iodinated contrast agents via the glomeruli creates potential for nephrotoxicity. Iodinated contrast nephrotoxicity is generally associated with a number of mechanisms (figure 5). Firstly, hypertonic solutions in the renal tubules reduce water reabsorption and this leads to tubular swelling, increased intra-renal pressure and a decrease in both renal blood flow and GFR (*12*). Concurrently, increased viscosity increases tubular pressure. Secondly, tubular cell damage results with a decrease in clearance of paraaminohippurate and increase in excretion of enzymes in the proximal tubules. Medullary hypoxia resulting from vasoconstriction and decreased blood flow also contribute to tubular cell damage. Tubular cell damage both reduces GFR and increases oxidative stress. Thirdly, cytotoxicity causes endothelial damage causing vasoconstriction and decreased GFR, and increases oxidative stress. Vasoconstriction can be exacerbated in diabetes and vasoconstrictive drugs (*12*).

Cardiovascular toxicity results in increased incidence or severity of cardiovascular adverse reactions to iodinated contrast agents. Underlying heart disease increases the risk of cardiovascular toxicity (*16*). Neurotoxicity associated with iodinated contrast agents results from an alteration in the blood brain barrier due to the hypertonicity (*16*). Clearly LOCM and IOCM agents

reduce this risk. Headache, confusion, seizures, altered consciousness, visual disturbances and dizziness are the most common signs of neurotoxicity.

Vasovagal reactions manifest as bradycardia and hypotension because the involuntary reflex slows heart rate and dilates blood vessels in the legs (*12*). Vasovagal reactions are not necessarily attributed to the contrast agent itself but a sympathetic nervous system response to fear or pain (*12*). Clearly anxiety can exacerbate this. With more blood in the legs and less in the brain, patients may get light headed and faint. Elevating the patients' legs in combination with 6-10 L/min of oxygen is generally adequate treatment.

Life threatening reactions usually occur in first 20 min post IV contrast (*12*). Indeed, 94-100% of severe or fatal adverse reactions to iodinated CT contrast agents occur within 20 minutes of contrast administration (*13*).

Management of Adverse Reactions

Prevention is better than cure. Prophylactic medications to reduce but not necessarily eliminate risk include 32mg of methylprednisolone orally 12 hours and 2 hours prior to contrast administration (Lasser protocol) and 50mg of diphenhydramine orally 1 hour before contrast administration plus 50mg of prednisone orally 13 hours, 7 hours and 1 hour before contrast administration (Greenberger protocol) (*11,13,17,18*). The Lasser protocol reduces adverse reactions from 9% to 6.4% for ionic contrast while the Greenberger protocol has been reported to decrease the incidence of adverse reaction to ionic contrast from 9% to 7% (*13*). Antihistamines are often used prophylactically in high risk patients without evidence of being able to reduce incidence of adverse reactions (*13*).

While the pharmacology associated with drugs in the crash cart / emergency trolley will be detailed in the next article in this series, here we briefly examine key medications that may be employed in the event of a serious or anaphylactoid

reaction to CT contrast agents. It should be noted that a crash cart / emergency trolley should be immediately available at all times in or immediately adjacent to the CT room where IV contrast is being used. One should also keep in mind that serious adverse effects may occur in the short period after the patient leaves the scanning room.

Salbutamol (albuterol) has been previously detailed (*5*) and functions as a beta-2 (β_2) receptor agonist to cause bronchodilation and relieve bronchospasm. The standard dose is 1-2 inhalations of 100mcg each with a third inhalation if necessary 1 minute after the second (*16,17,19*). This same dose can be given prophylactically. Patients with bronchospasm should also be supported with 10L/min of oxygen delivered via a mask (*13,17*). Atropine is a parasympatholytic agent that can be used to treat bradycardia in a vasovagal reaction. The standard dose is 0.6-1.0mg IV repeated every 3-5 min as needed to a maximum of 3mg (*13,16-19*). Elevation of the patient's legs and delivery of oxygen (10L/min) should be used to support the self-limiting vasovagal patient (*13,17*). Diphenhydramine (Benadryl) is a histamine-1 (H_1) inhibitor but antihistamines (*4*) block further histamine mediated reactions but do not stop histamine mediated reactions already underway. It should only be used for mild urticaria or prophylaxis with doses of 25-50mg orally or IM, or 25mg IV being standard (*13,17*). This dose can cause drowsiness. Epinephrine (adrenaline) is a sympathetic agonist with alpha (α) and beta (β) receptor activity. α receptor agonism with epinephrine causes peripheral vasoconstriction which can help with severe urticaria, facial edema and laryngeal edema (*13,16,19,20*). β_1 receptor agonism produces inotropic and chronotropic effects (*5*) so should be used with caution in known heart disease. B_2 receptor agonism causes bronchodilation so epinephrine can be used to treat bronchospasm (*13,16,17,19,20*). Doses of epinephrine are typically 0.1-0.3mg (1mg/mL or 1:1000) subcutaneous / 0.3mg IM via EpiPen if the patient is not hypotensive, or 0.1mg (0.1mg/mL or 1:10000) IV over 3-5 minutes repeated as needed up to a maximum of 1mg if the patient is hypotensive (*13,16,17,19,20*). Diazepam is a benzodiazepam that can be used to

treat seizures if needed (*4*) utilizing an IV dose of 5-10mg to a maximum of 30mg as required. Lorazepam is an alternative benzodiazepam for seizures especially in pediatric patients with a dose of 0.01mg/kg IV. Nitroglycerin (*5*) is a vasodilator that decreases oxygen demand which can be used to treat acute angina. The dose can be anyone of the following; one 300 to 600 mcg sublingual tablet under the tongue, one or two sprays of 400 mcg each directed onto or under the tongue, or 2-3mg buccal tablet placed between the upper lip and gum. Sublingual tablet or spray doses can be repeated if necessary.

In the case of generalized anaphylaxis-like symptoms, epinephrine should be used. Doses are typically 0.1-0.3mg (1mg/mL or 1:1000) subcutaneous / 0.3mg IM via EpiPen if the patient is not hypotensive, or 0.1mg (0.1mg/mL or 1:10000) IV over 3-5 minutes repeated as needed up to a maximum of 1mg if the patient is hypotensive (*13,16,17,19,20*). A B_2 agonist can be added for bronchospasm. Saline infusion should be used for hypotension.

Nausea and vomiting are self limiting and patients need to be observed for 30 minutes while keeping IV access open (*13*). If nausea and vomiting continue, antiemetic medications could be considered (*13*). Antiemetics are a class of medication that block neurotransmitters (eg. acetylcholine, histamine, dopamine, substance P and 5-hydroxytryptamine) responsible for nausea and vomiting in the emetic center in the medulla, vestibular apparatus, chemoreceptor trigger zone in the fourth ventricle, and higher brain centers that relay sensory inputs (*19*). Specific examples of medications include metoclopramide for D_2 receptor antagonism, hyoscine hydrobromide for muscarinic receptor antagonism, promethazine for H_1 receptor antagonism, ondansetron for 5-HT_3 receptor antagonism and aprepitant for NK_1 receptor antagonism (*19*). The recumbent position helps minimize aspiration.

Extravasation

Extravasation of iodinated contrast agents involves delivery of the contrast extravascularly due to human error, canula dislodgement or leakage. While well recognised, true incidence of extravasation is hard to reliably determine but several large studies report an incidence less than 1% (*10*). Extravasation of iodinated contrast agents typically causes self-limiting symptoms like pain, erythema, and swelling (*21*). In severe reactions, skin ulceration and necrosis, or the development of compartment syndrome may occur (*21,22*). While more severe reactions tend to occur with larger volumes of extravasated HOCM or ionic contrast, they can occur with small volumes of LOCM and non-ionic contrast (*21*). The peak reactions occur at 24-48 hours post IV contrast administration.

Once again, prevention is a better option than therapy. Key strategies to minimise the risk of extravasation include, without being limited to (*23,24*):

- reliable IV access that is tested prior to contrast administration,
- decrease flow rates if the protocol allows in high risk patients,
- limit flow rates to 3mL/sec for large veins and 1.5mL/sec for the hand or wrist,
- monitor the infusion site directly for the first 15 seconds of the infusion,
- communicate with the patient to report immediately any unusual sensations at the IV site during contrast administration, and
- immediately stop the infusion if there is concern regarding extravasation.

If extravasation of iodinated contrast agents does occur, management will depend on the patient symptoms and volume of extravasation. The infusion should be stopped immediately, and the IV site elevated with a cold compress applied (*11,25*). For small volumes and self-limiting symptoms, the patient should be monitored in the CT department for 2-4 hours (*11,25*). For large volumes (30-100mL), blistering or ulceration, altered perfusion, a change in sensation, or worsening pain or swelling after the 2-4 hour monitoring window, the patient

should be referred to the local emergency department for surgical consultation (*11,25*).

Interactions

Iodinated contrast agents are not highly active pharmacologically, however, interactions with medications the patient may be taking is possible (*26*). Prevention is a good practice and this comes with a thorough patient history, an awareness of drugs needing precautions, and by not administering contrast through the same line as medications (*26*). Iodinated contrast agents have anticoagulant properties (less so for non-ionic) and prolong coagulation time so can potentiate the effects of anticoagulant (eg. heparin and warfarin), anti-platelet (eg. aspirin and NSAIDs) and fibrinolytic medications (eg. urokinase) (*12,16,26*). Metformin can have additive effects associated with iodinated contrast toxicity (*12,16,26*). Beta blockers increase the risk and severity of anaphylactoid reactions (*12,16*). Calcium channel blockers can potentiate hypotensive effects of iodinated contrast agents (*12,16*). Diuretics can have a cumulative effect with iodinated contrast agents for diuresis and increase the risk of nephrotoxicity (*12,16,26*). Nephrotoxic medications like NSAIDs and gentamicin can potentiate the renal effects of iodinated contrast (*26*). Adverse reactions to iodinated contrast agents are more likely if the patient is taking immunomodulator medications (*12,16,26*). Allergic reactions or symptoms of a similar nature are more likely in patients taking beta blockers, interleukins and interferons (*26*). Patients taking beta blocker medications have a three-fold increase in risk for anaphylactoid adverse reactions to iodinated contrast (*26*). Any medication with that relies on renal elimination may have increased retention and activity and those medications with a narrow therapeutic index may be susceptible to toxicity (*26*). Synergistic effects between iodinated contrast media and calcium channel blockers and digoxin are possible, especially with ionic HOCM (*26*).

Contraindications and Precautions

A number of medications are relatively contraindicated with ionic contrast media because they will crystalize and form precipitates including cimetidine, diazepam, diphenhydramine, ethanol, meperidine, papaverine, promethazine and protamine sulfate (*12,16*). Clearly some of these medications are prescribed for prophylaxis

or management of adverse reactions and so caution is suggested, especially administration through the same IV line. Non-ionic contrast agents do not share this incompatibility. Caution should also be exercised when using iodinated contrast agents in patients medicated with known nephrotoxic drugs including angiotensin converting enzyme inhibitors (ACEI), acyclovir, aminogylcosides, amphotericin, anti-neoplastics, cyclosporin, furosemide, lithium, metformin, methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs), tacrolimus and vancomycin (*12,16*). Creatinine levels may warrant assessment before progression with CT contrast in these patients. As outlined above, there are numerous factors that identify a patient as having a higher risk of adverse reaction and while caution should be exercised, none are absolute contraindications. Perhaps the highest risk group are those patients with a GFR less than 30 ml/min/1.73m^2. In this group iodinated CT contrast should not be administered unless the patient is on dialysis and anuric or the diagnostic benefits outweigh the risk. LOCM, non-ionic, dimer based contrast with low iodine concentration are lower risk options for patients at increased risk of adverse reactions when the benefit of the contrast procedure warrants iodinated contrast CT.

MRI CONTRAST

Introduction to MRI Contrast

There are a number of different types of contrast media employed in MRI, however, the vast majority used clinically and the focus of this article are the T1 paramagnetic contrast agents associated with gadolinium. Worldwide, 40-50% of MRI procedures are undertaken with contrast (*27*). Nonetheless, it is important to highlight key aspects of the five classes of MRI contrast agents (*28*):

- T1 agents are discussed below.
- T2/T2* agents are superparamagnetic nanoparticles comprised of iron oxides that shorten the relaxation times of T2/T2* (*28*). While paramagnetic contrast agents increase proton signal, superparamagnetic / ferromagnetic contrast agents destroy the signal (negative contrast) (*28*). For example, MRI contrast might be achieved by a T2/T2* contrast agent destroying the signal for liver but not from a liver metastases.
- CEST agents refer to Chemical Exchange Saturation Transfer (*28*). CEST agents are chemicals that create MRI contrast by transferring saturated protons to the bulk water pool (*28*).
- ^{19}F nuclei are not only naturally occurring fluorine but also the most sensitive spin (resonance) in MRI after hydrogen (*28*). As a result, ^{19}F nuclei are readily detected by MRI (*28*). The barrier to using ^{19}F nuclei instead of ^{18}F nuclei in radiopharmaceuticals is that in nuclear medicine the tracer principle is adopted while MRI requires large (potentially toxic) concentrations; 1 fluorine atom versus 20 or more per structure. Instead, ^{19}F nuclei are incorporated into perfluorocarbon nanoparticles (PFCs), avoiding toxicity by encapsulation of many perfluorocarbon molecules in phospholipid encapsulated nanoparticle.
- Hyperpolarised probes use polarization techniques (like dynamic nuclear polarization) to increase (up to five orders of magnitude) sensitivity to the spin energy levels (*28*). Unfortunately, despite excellent sensitivity, these agents require fast injection and target accumulation to overcome signal decay (*28*).

Paramagnetic substances have one or more particles (protons, neutrons or electrons) with a spin that is not cancelled by another similar particle with an opposite spin. Magnetic dipole moments of unpaired electrons are very much larger than those of protons or neutrons, so that the local magnetic fields generated by unpaired electrons are very strong (*28*). Substances that have unpaired electrons, such as gadolinium, are very effective paramagnetic contrast enhancers (*28*). When paramagnetic ions are added to water, the relaxation of water molecules is enhanced in the vicinity of the paramagnetic substance (*27,28*). Both T1 and T2 relaxation times are then reduced. It is not the actual contrast agent which alters the intensity of the image but the presence of the contrast agent alters the relaxation characteristics of adjacent protons, thus indirectly affecting the intensity (*28*). While gadolinium is technically a paramagnetic agent as a result of its unpaired electrons, this characteristic is not the basis of T1 contrast enhancement (*28,29*). It is the dipole-dipole interaction that influences T1 relaxation (*27-29*). Gadolinium contains seven unpaired electrons, making these compounds strongly paramagnetic (*27*). Gadolinium is a lanthanide because the inner electron shells of its atomic structure are not be filled. In its ionized form (Gd^{3+}), gadolinium donates electrons from other sub-shells, leaving the seven 4f electrons unpaired and this property ensures paramagnetic behavior after chelation.

Properties of gadolinium MRI Contrast

There are a number of key properties of gadolinium contrast agents that influence their behaviour, efficiency and their adverse reaction risk / profile. There is an interplay between these properties that optimise the degree of enhancement and its tolerability including (*29*) (table 3):

- chemical structure,
- osmolality,
- viscosity,
- iconicity, not to be confused with demetallation (de-chelation),

- relaxivity,
- half clearance rate, and
- dose.

Gadolinium is tightly chelated into a complex chemical structure that can be linear or macrocyclic (figure 6). Macrocyclic chemical structures employ DOTA chelation. The chemical structure prevents heavy metal toxicity because the tight chelation prevents cellular uptake of the toxic free gadolinium ion (*27*). Collectively, the chemical structure and chelation of gadolinium enhance renal elimination and maintain distribution in the extravascular space (*27,29*). Regardless of chemical structure, the pharmacodynamics and pharmacokinetics are the same (*29*). The standard gadolinium contrast dose is 0.1mmol/kg (*27,29*). This dosage primarily influences the T1 relaxation time but higher doses may increase effect of T2 relaxation.

Relaxivity measures the degree to which a given amount of contrast agent shortens T1 or T2 so higher relaxivity equates to better enhancement. Relaxivity refers to the contrast agents' change in relaxation rates with changes in concentration. Largely the early generation gadolinium contrast agents shared the same T1 relaxivity while later generation contrast agents have up to 50% higher T1 relaxivity at 1.5T (*29*).

As with iodinated contrast agents, osmolality contributes to the incidence of non-anaphylactoid adverse reactions mediated by endothelial damage, movement of fluid amongst compartments, and cell deformation. Adverse effects attributable to osmolality include pain, flushing, nausea, and vomiting (*12*). Contrast osmolality higher than blood results in movement of water from interstitial spaces into the vascular compartment which causes increased blood viscosity, endothelial damage, hypervolemia, vasodilation, edema with neurotoxicity, decreased myocardial contractility and toxicity (*6,29*). Gadolinium contrast is administered in much lower doses than iodinated contrast in CT and as such, the alteration to

plasma osmolality is very low, reducing impact of adverse reactions by comparison (*27*). Nonetheless, when large gadolinium contrast doses are to be administered, low osmolality agents should be employed (*27*).

The viscosity of gadolinium contrast agents is the flow friction, resistance or thickness of the contrast media (*8,12*). Gadolinium contrast is generally of similar viscosity to blood at body temperature (37^{o}C) (*29*). Viscosity plays an important role in renal tolerance, with near serum viscosity reducing the risk of contrast induced nephrotoxicity associated with iodinated contrast media. Viscosity of gadolinium contrast agents is not considered a significant concern for adverse reactions (*27,29*).

Ionic gadolinium CT contrast agents dissociate into ion pairs while non-ionic do not (*29*). Ionic contrast may increase the risk of some adverse reactions like cardiac arrhythmia (*29*). A combination of ionic and high osmolar gadolinium contrast increases the adverse cardiovascular effects and the hemodynamic changes present a risk to patients with coronary artery disease (*29*). Like the effects of osmolality, the low dose of gadolinium contrast compared to iodinated CT contrast, even with ionic MRI contrast, the ionic charge of the gadolinium complex is not considered significant in terms of safety and risk of adverse reactions (*27*).

Mechanism of Action

As with iodinated CT contrast, MRI contrast agents provide image contrast without altering biological function (*29*). Unlike iodinated contrast agents in CT, MRI contrast agents are not directly detected but rather indirectly by influencing the nuclear magnetic relaxation time of water (*27,29*). While gadolinium shortens the relaxation time constants for T1, T2 and T2* in adjacent protons (water) in tissues, it is the shortening of T1 that is the target of MRI imaging (*27,29*). As a result, rapid acquisition of T1 weighted MRI images will have an increased signal from contrast enhanced tissues (*29*). MRI physics is too complex to describe in

the context of this article, but some assumed knowledge is necessary to understand the mechanism of action. Nonetheless, figure 7 provides a schematic representation of T1 and T2 contrast enhancement. Specifically, gadolinium causes T1 shortening through dipole-dipole interactions with protons (*27,29*).

Pharmacokinetics

Gadolinium is a heavy metal toxin when free invivo as an ion, yet the risk of adverse reaction is low and the majority of adverse reactions being mild (*29*). This is primarily the result of the chemical stability associated with gadolinium chelation (much the same way 68Ga, 99mTc and other radiometals are chelated in radiopharmaceuticals). These chelates also overcome the potential consequences of the long biological half life of free gadolinium (*29*). Consequently, gadolinium contrast agents are almost exclusively eliminated unchanged (no metabolism) via the kidneys with a half clearance time in normal renal function of 1.5-2 hours (*29*). Renal clearance occurs without secretion or reabsorption (*27,31*). Gadolinium contrast demonstrates 85% elimination by 4 hours after IV administration, 98% elimination by 24 and 100% by 48 hours post administration, but renal dysfunction prolongs retention (*27,31*).

Extracellular gadolinium chelates have pharmacokinetic properties similar to iodinated CT contrast media (*27,31*). After IV administration, gadolinium contrast agents are rapidly cleared from intravascular space to extravascular space with a distribution equivalent to extracellular water (*27,31*). They show no plasma protein binding and they do not cross intact blood brain barrier (*27,31*). Like iodinated contrast, gadolinium clearance is biphasic with initial distribution with a 4 minute half life followed by the aforementioned 1.5-2 hour elimination half life (*27,29,31*). Gadolinium contrast is best illustrated with a two-compartment model as illustrated for iodinated contrast (figure 3). Gadolinium contrast can enter and wash out of normal tissues and diseased tissues at different rates which will change T1 and T2 relaxation times between those tissues (*27,31*).

Contraindications and Precautions

Gadolinium contrast agents cross the placenta and undergo fetal excretion via the kidneys. The excreted contrast remains in the amniotic fluid for a protracted period of time where it could undergo demetallation (de-chelation) into free gadolinium and expose the fetus lungs and gut (*29*). Consequently, gadolinium contrast is contraindicated during pregnancy, especially the first trimester (*27*). If gadolinium contrast is to be used during pregnancy, macrocyclic varieties should be employed (*27*). While gadolinium contrast agents are also excreted in breast milk, the dose to the infant is a fraction of that of the mother and is excreted after oral absorption in feces (*29*). There is no need for cessation of breast feeding (*27*) although a cautious approach would include expressing and discarding for 6 hours post IV gadolinium contrast.

While gadolinium contrast agents are considered safe and biologically inert, they are more nephrotoxic than iodinated contrast agents in the equivalent dosage (*27*). High doses in impaired renal function is contraindicated (*16,27*). Acute renal failure occurs in 3.5% of cases of abnormal creatinine levels (*27*). Gadolinium contrast is contraindicated in patients with a GFR below 30 mL/min/1.73m^2 or where renal function is acutely deteriorating (*16*). Previous anaphylactoid / hypersensitivity reactions to gadolinium contrast should be treated with caution (*16*). Pre-existing NSF is also a contraindication (*16*). Caution should be exercised in gadolinium contrast use in patients with moderate renal dysfunction, epilepsy, hypotension, a history of hypersensitivity, asthma or allergic respiratory disorders (*16*). Caution should be exercised in patients with severe cardiovascular disease or drug induced arrythmia (*16*).

Adverse Reactions

Adverse effects to gadolinium contrast agents are very uncommon with an incidence generally reported in the range 1.5-2.4% (*27,29*). Most adverse reactions are considered mild and more commonly include mucosal reactions, urticaria, vomiting, change in taste, local warmth, local pain, headache,

paresthesia and dizziness (figure 4) (*16,27,29,30*). Vasodilation and injection site discomfort are also possible (*29*). The risk of an adverse reaction increases in patients with asthma, allergies, and a history of contrast reaction to gadolinium or iodine (*27,29*). If appropriate, adverse reactions should be reported to the regulatory authority.

In a study of 17767 patients undergoing cardiac MRI with gadolinium contrast, there were only 0.17% of patients who experienced adverse reactions and 100% of those were mild in nature (*32*). Furthermore, the adverse reaction rate between different agents varied between 0.06% to 0.47% (*32*). In another study with 194400 ionic, linear gadolinium contrast injections, there was a 0.1% incidence of adverse reactions of which 83.8% were classified as mild, 13.7% moderate and 2.4% severe (5 cases) (*33*).

Acute hypersensitivity reactions occur within 1 hour of contrast administration and in 0.1% of patients and include mild pruritis (itching) and urticaria (hives) (*34*). It should be noted that a prior gadolinium contrast agent hypersensitivity reaction is associated with 30% risk of reaction to subsequent gadolinium administrations and with greater severity (*34*). Patients can experience moderate hypersensitivity reactions and include bronchospasm, laryngeal edema, facial edema, tachycardia, angioedema, hypotension, arrhythmia and widespread urticarial (*16,34*). Severe anaphylactoid reactions has an incidence of 0.005% and fatal reactions 0.0003%. An increased risk of a hypersensitivity reaction to gadolinium contrast is associated with females, those with allergies or asthma, and for those having prior gadolinium contrast administrations (*34*).

The adverse reaction profile of gadolinium contrast agents is uniform across the range of agents (*27,29*). This may seem a little surprising given the variability in ionicity, viscosity and osmolality known to be major contributors to adverse reactions in iodinated contrast media. This is likely to reflect actual differences that can not be distinguished statistically. For example, there is a 10-fold

difference in the incidence of urticaria across a range of gadolinium contest media from 0.2% to 2% but data does not permit a statistically significant difference to be reported (*29*). Likewise, the incidence of nausea ranges from 1.2% to 3.2% across the range of contrast agents (*29*). Faster injection rates (eg. MRI angiography) have been reported to demonstrate higher incidence of nausea (*29*). Acute reactions occur even with antihistamine or corticosteroid premedication (*33*).

Gadolinium MRI contrast is not generally considered nephrotoxic and this relates to the low viscosity and comparative low dose (*27,29*). Contrast induced nephrotoxicity for iodinated contrast agents (figure 5) is driven by viscosity and osmolality. Gadolinium contrast has near serum viscosity and sufficiently low doses that blood and tissues remain isotonic after contrast. Gadolinium contrast does, however, have higher nephrotoxicity than iodinated CT contrast for equivalent dosage (*27*).

Free gadolinium (Gd^{3+}) is highly toxic and this relates, in part, to cellular inhibition of calcium (Ca^{2+}) at calcium channels (*27,31,35*). As outlined in a previous article in this series (*5*), alteration to influx of calcium interferes with muscle contraction (eg. cardiac force of contraction), vascular smooth muscle vasoconstriction and bronchial smooth muscle bronchoconstriction. Free gadolinium can also depress the reticuloendothelial system, including inhibition of phagocytosis (*27,31*). The LD50 for non-chelated gadolinium is 0.35mmol/kg whole DOTA chelation increases this to 10.6 mmol/kg (*31*). Recent investigations have shown increased signal intensities in the dentate nucleus and globus pallidus suggesting concentration of free gadolinium (*35*). The clinical and adverse implications of this finding are currently unclear.

Nephrogenic Systemic Fibrosis

Gadolinium has an excellent safety record, however, patients are at risk of developing nephrogenic systemic fibrosis (NSF) (*29,36*). Unfortunately, NSF is

irreversible with no treatment and associated with progressive movement, swallowing and breathing difficulties (*29,36,37*). NSF patients may develop subcutaneous edema causing hard, erythematous plaques of skin with or without hyperpigmentation, papules, blistering and ulceration (*37*). Patients present with symptoms of pain, severe pruritus, paresthesia, flexion contractures and unstable hypertension (*37*). The incidence of NSF is very low and has decreased substantially since awareness to the risk was uncovered. An evaluation of over 185 million gadolinium contrast injections revealed less than 1000 cases of NSF (0.0005%) (*37*). This varied amongst contrast agents from a 1 in 2 million risk to a 1 in 50000 risk (*37*). Linear non-ionic chelates are considered the highest risk while macrocyclic chelates low risk and linear ionic chelates the middle ground of risk (*37*). Macrocyclic gadolinium contrast exhibit less demetallation and ionic gadolinium contrast also tends to be more tightly bound (*36*).

A history of renal dysfunction or significant infirmity increases the risk of developing NSF (*29,36*). Gadolinium contrast is contraindicated in patients at high risk of NSF (*29,36*). High risk patients meet one or more of (*29,36*):

- kidney or liver transplant with GFR less than 60 mL/min/1.73m^2, or
- GFR less than 30 mL/min/1.73m^2, or
- acute renal failure, and
- have one or more of the following comorbid conditions; major infection, vascular ischemia of extremities, vascular thrombosis, major surgery, major vascular procedure or multi-organ system failure.

Given the long biological half life of free gadolinium and the very long retention of lanthanides in bone, it is important to consider the life-long burden of gadolinium, especially in those have multiple contrast studies over their life span (*31*).

The vast majority, if not all, NSF cases after gadolinium contrast have significant renal dysfunction prior to administration (*36,37*). The worse the renal function at the time of administration the higher the risk of NSF (*36*). The greater the total contrast dose the greater the risk and severity of NSF (*36*). The vast majority of

patients who received gadolinium contrast, despite having significant renal dysfunction, do not get NSF (*36*).

NSF usually develops clinically within days to months following gadolinium exposure, although rare cases have been reported years later (*36*). Renal dysfunction causes a prolonged elimination half life and the retention of gadolinium increases the predisposition of the Gd^{3+} to be displaced in the chelate by other metal cations like iron (Fe^{3+}), copper (Cu^{2+}), zinc (Zn^{2+}) or calcium (Ca^{2+}) in a process called transmetallation (*31*). At the same time, a number of anions can compete for the Gd^{3+} ligand including phosphate, carbonate, hydroxide and citrate (*31*). The free gadolinium ion (Gd^{3+}) can then be deposited in skin and soft tissue to precipitate NSF (*31*). Procedural changes, improved contrast agents and pre-screening high risk patients has virtually eliminated this iatrogenic condition. In the absence of severe renal dysfunction, free gadolinium can manifest as gadolinium induced plaques in the extremities. Transmetallation of the cation and exchange of the anion may cause spurious pseudo-hypocalcemia (*31*).

Management of Adverse Reactions

Given the absence of treatment for NSF, the remainder of the adverse reactions can and should be managed in the same way outlined above for iodinated contrast based on the type of adverse reaction and symptoms (figure 4).

Extravasation

Fast mechanical injectors with large volumes for MRI contrast agents increases the risk of full or partial dose extravasation (*29*). Given the hypertonic nature of gadolinium contrast media, the effects and treatment are the same as those outlined above for iodinated CT contrast. Indeed, the prevention strategies and risk factors are also similar.

Interactions

Specific interactions between gadolinium contrast agents and medications have not been widely evaluated or reported (*26*). The common properties of gadolinium contrast and iodinated contrast (iconicity, osmolality) present a similar interaction profile, although the lower doses of gadolinium truncate interaction risk. Like iodinated contrast agents, gadolinium contrast agents are not highly active pharmacologically (*26*). Prevention relies on a thorough patient history, an awareness of drugs needing precautions, and by not administering contrast through the same line as medications (*26*). Ionic gadolinium contrast agents have anticoagulant properties and both ionic and non-ionic can prolong coagulation time so this can potentiate the effects of anticoagulants (eg. heparin and warfarin), anti-platelet (eg. aspirin and NSAIDs) and fibrinolytic medications (eg. urokinase) (*26*).

Gadolinium contrast agents are not considered a high risk of nephrotoxicity so do not substantially increase the bioavailability of renally eliminated medications, however, nephrotoxic medications like NSAIDs and gentamicin can compound renal dysfunction to increase the risk of NSF (*26*). Adverse reactions to gadolinium contrast agents are more likely if the patient is taking immunomodulator medications (*26*). Allergic reactions or symptoms of a similar nature are more likely in patients taking beta blockers, interleukins and interferons (*26*). Synergistic effects between gadolinium contrast media and calcium channel blockers and digoxin are possible (*26*). Higher osmolality gadolinium contrast agents used for cerebral angiography lower the seizure threshold of antipsychotics, thiozanthines, antidepressants and analeptics (*26*).

From a nuclear medicine perspective, gadolinium contrast agents in the 72 hours prior to ^{67}Ga-citrate administration is known to alter biodistribution; evident in more defined skeletal accumulation of the ^{67}Ga. Gallium is an iron analogue and can readily undergo transmetallation with gadolinium and exchange between citrate and the chelate can also occur.

CONCLUSION

CT and MRI contrast are unique interventions that demand an expanded skill set and understanding of basic and applied pharmacology (*1-5*). An insight into the complexities of both iodinated and gadolinium contrast enhances practice and patient safety. Specifically, command of adverse reactions is a key skill required for capability in CT or MRI, and ensures the nuclear medicine technologist meets the minimum capabilities for their scope of practice (*38*).

References

1. Currie G. Pharmacology part 1: introduction to pharmacology and pharmacodynamics. *Journal of Nuclear Medicine Technology*, 2018;46:81-86.
2. Currie G. Pharmacology part 2: introduction to pharmacokinetics. *Journal of Nuclear Medicine Technology*, 2018;46:?? *in press*.
3. Currie, G 2018, Pharmacology part 3A: interventional medications in renal and biliary imaging, *Journal of Nuclear Medicine Technology*, *in press*.
4. Currie, G 2018, Pharmacology part 3B: less commonly used interventional medications and adjunctive medications in general nuclear medicine, *Journal of Nuclear Medicine Technology*, *in press*.
5. Currie, G 2018, Pharmacology part 4: nuclear cardioloogy, *Journal of Nuclear Medicine Technology*, *in press*.
6. Bourin M, Jolliet P, Ballereau F. An overview of the clinical pharmacokinetics of x-ray contrast media. *Clin Pharmacokinet*, 1997;32:180-193.
7. Meurer K, Kelsch B, Hogstrom B. The pharmacokinetic profile, tolerability and safety of the iodinated, non-ionic, dimeric contrast medium Iosimenol 340 injection in healthy human subjects. *Acta Radiologica*, 2015;56:581-586.
8. Greenen RWF, Kingma HJ, van der Molen AJ. Contrast-unduced nephropathy: pharmacology, pathophysiology and prevention. *Insights Imaging*, 2013;4:811-820.
9. Block JH, Beale JM. *Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry* (12th ed.). Philadelphia: Lippincott Williams & Wilkins; 2011.
10. Pasternak JJ, Williamson EE. Clinical pharmacology, use, and adverse reactions of iodinated contrast agents: a primer for non-radiologists. *May Clin Proc*, 2012;87:390-402.
11. Namasivayam S, Kalra MK, Torres WE, Small WC. Adverse reactions to intravenous iodinated contrast media: a primer for radiologists. *Emerg Radiol*, 2006;12:210-215.
12. Costa N. Understanding contrast media. *J Infusion Nursing*, 2004;27:302-312.
13. Iyer RS, Schopp JG, Swanson JO, Thapa MM, Phillips GS. Safety essentials: acute reactions to iodinated contrast media. *Canadian Association of Radiologists Journal*, 2013;64:193-199.
14. Bae KT. Intravenous contrast medium administration and scan timing at CT: considerations and approaches. *Radiology*, 2010;256:32-61
15. Seibert JA, Boone JM. X-ray imaging physics for nuclear medicine technologists. Part 2: x-ray interactions and image formation. *J Nucl Med Technol*, 2005;33:3-18.
16. Sweetman SC (Ed.). *Martindale the complete drug reference* (26th ed.). Chicago: Pharmaceutical Press; 2009.

17. Morzycki A, Bhatia A, Murphy KJ. Adverse reactions to contrast material: a candian update. *Canadian Association of Radiologists Journal*, 2017;68:187-193.

18. Namasivayam S, Kalra MK, Torres WE, Small WC. Adverse reactions to intravenous iodinated contrast media: an update. *Curr Probl Diagn Radiol*, 2006;July/August:164-169.

19. Bryant, B, Knights, K & Salerno, E 2007, Pharmacology for Health Professionals, 2nd edn, Mosby Elsevier, Sydney.

20. Rang, H, Dale, M, Ritter, J & Flower, R 2008, Rang and Dale's Pharmacology, 6th edn, Churchill Livingston, London.

21. Cohan RH, Ellis JH, Garner WL. Extravasation of radiographic contrast material: recognition, prevention, and treatment. *Radiology*, 1996; 200: 593-604.

22. Ayre-Smith G. Tissue necrosis following extravasation of contrast material. *J Can Assoc Radiol*, 1982; 33: 104.

23. Jacobs JE, Birnbaum BA, Langlotz CP. Contrast media reactions and extravasation: relationship to intravenous injection rates. *Radiology*, 1998; 209: 411-6.

24. Federle MP, Chang PJ, Confer S, Ozgun B. Frequency and effects of extravasation of ionic and nonionic CT contrast media during rapid bolus injection. *Radiology*, 1998; 206: 637-40.

25. Wang CL, Cohan RH, Ellis JH, Adusumilli S, Dunnick NR. Frequency, management, and outcome of extravasation of nonionic iodinated contrast medium in 69,657 intravenous injections. *Radiology*, 2007; 243: 80-7.

26. Morcos SK, Thomsen HS, Exley CM. Contrast media: interactions with other drugs and clinical tests. *Eur Radiol*, 2005;15:1463-1468.

27. Bellen MF, van der Molen. Extracellular gadolinium-based contrast media: an overview. *Euro J Radiology*, 2008;66:160-167.

28. Terreno E, Aime S. MRI contrast agents in pharmacological research. Frontiers in pharmacology, 2015;6:290.

29. Lin SP, Brown JJ. MR contrast agents: physical and pharmacologic basics. *J MRI*, 2007;25:884-899.

30. Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate allergic reactions to gadolinium-based contrast agents: a systemic review and meta-analysis. *Radiology,* 2018; 286:471-482.

31. Abraham JL, Thakral C. Tissue distribution and kinetics of gadolinium and nephrogenic systemic fibrosis. *Euro J Radiology*, 2008;66:200-207.

32. Bruder O, Schneider S, Nothnagel D, Pilz G, Lombardi M, Sinha A, Wagner A, Dill T, Frank H, van Rossum A, Schwitter J, Nagel E, Senges J, Sabin G,

Sechtem U, Mahrholdt H. Acute adverse reactions to gadolinium-based contrast agents in CMR. *JACC: cardiovascular Imaging*, 2011;4:1171-1176.

33. Aran S, Shaqdan KW, Abujudeh HH. Adverse allergic reactions to linear ionic gadolinium-based contrast agents: experience with 194,400 injections. *Clinical radiology*, 2015;70:466-475.
34. Jung JW, Kang HR, Kim MH, Lee W, Min KU, Han MH, Cho SH. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. *Radiology*, 2012; 264:414-422.
35. Radbruch A, Weberling LD, Kieslich PJ, Eidel O, Burth S, Kickingereder P, Heiland S, Wick W, Schlemmer HP, Bendszus M. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology*, 2015;275:783-91.
36. Kanal E. Gadolinium based contrast agents (GBCA): safety overview after 3 decades of clinical experience. *Magnetic resonance imaging*, 2016; 34:1341-1345.
37. Khawaja AZ, Cassidy DB, Shakarchi JA, McGrogan DG, Inston NG, Jones RG. Revisiting the risks of MRI with gadolinium based contrast agents – review of literature and guidelines. *Insights Imaging*, 2015;6:553-558.
38. SNMMI-TS Scope of Practice Task Force. Nuclear medicine technologist scope of practice and performance standards. *Journal of Nuclear Medicine Technology*, 2017;45:53-64.

LIST OF TABLES

Table 1: Optimizing the key properties of IV CT contrast agents has resulted in an evolution of CT contrast to those that are easier to use with low IV toxicity and less adverse effects (frequency and severity) (*6,8,12*).

Contrast	Iodine Concentration mg/mL	Osmolality mOsm/kg water	Viscosity mPa/s (37°C)
Ionic monomer (HOCM)	Up to 400	1400-2100	
Ionic dimer (HOCM)	320	600	
Non-ionic monomer (LOCM)	Up to 350	600-800	
Non-ionic dimer (IOCM)	320	290	
Human serum	3.2-4	290	1.5-2.0
Ionic monomers			
Amidotrizoic acid (*Urografin*)	146	1690	8.5
Amidotrizoate-meg (*Angiografin*)		1530	
ioxitalaminic acid (telebrix)	350	2130	7.5
Non-ionic monomers			
Iohexol (*Omnipaque*)	240, 300, 350	500, 690, 880	3.3, 6.1, 10.6
iopamidol (*Isovue*)	200, 300, 370	413, 616, 796	2.0, 4.7, 8.6
ioxilan (*Oxilan*)	350	695	4.6
iopromide (*Ultravist*)	370	780	9.5
ioversol (*Optiray*)	320	702	5.8
iomeprol (*iomeron*)	350	618	7.5
iobitridol (*xenetix*)	350	915	10.0
Ionic dimers			
ioxaglate (*Hexabrix*)	320	580	7.5
Nonionic dimers			
iodixanol (*Visipaque*)	320	290	11.4
iotrolan (*isovist*)	300	320	8.1

Table 2: Incidence of adverse reactions to iodinated IV contrast agents (*10-13,16-18*).

Reaction type	**Ionic**	**Non-ionic**	**Ionic HOCM**	**Non-ionic LOCM / IOCM**
Mild	15%	3%		
Moderate	1-2%	0.2-0.4%		
Severe	0.2%	0.04%	0.22%	0.04%
Fatal	0.0006%	0.0006%		
Overall			13%	3%
Delayed	2-4% for non-ionic dimer	0.5-1% for ionic and non-ionic monomers	12.5% for CT with IV contrast	10% for CT without IV contrast
Extravasation	0.04-0.2% for mechanical power injectors			
Contrast induced nephropathy	1-3% in normal renal function	12-27% in renal impairment	50% in diabetic nephropathy	

Table 3: A comparison of the key properties of the main gadolinium contrast agents. With the exception of Primovist, the dosage is 0.1 mmol/kg. Primovist dosage is 0.025 mmol/kg (*27,29,30*).

Contrast agent	Structure	Ionicity	Clearance $T_{0.5}$ (hours)	Osmolality (mOsm/kg water)	Viscosity at 37ºC (cps)	T1 Relaxivity (L/mmol-s)
Gadopentate dimeglumine (*Magnevist*, Gd-DTPA)	Linear	Ionic	1.6	1960	2.9	4.1
Gadoteridol (*ProHance*, Gd-HP-DO3A)	Macrocyclic	Non-ionic	1.57	630	1.3	4.1
Gadodiamide (*Omniscan*, Gd-DTPA-BMA	Linear	Non-ionic	1.3	789	1.4	4.3
Gadoversetamide (*OptiMARK*, Gd-DTPA-BMEA)	Linear	Non-ionic	1.73	1110	2.0	5.2
Gadobenate dimeglumine (*MultiHance*, Gd-BOPTA)	Linear	Ionic	1.2-2	1970	5.3	6.3
Gadoterate (*Dotarem*, Gd-DOTA)	Macrocyclic	Ionic	1.6	1350	2.4	3.6
Gadobutrol (*Gadavist*, Gd-BT-DO3A)	Macrocyclic	Non-ionic	1.81	1603	5.0	5.2
Gadoxetate (*Eovist* or *Primovist*, Gd-EOB-DTPA)	Linear	Ionic	0.93	688	1.2	6.9
Gadofosveset (*Ablavar*)	Linear	Ionic		1110	3.0	19
Blood				290	1.5-2	

LIST OF FIGURES

Figure 1: The chemical structure of iodinated CT contrast agents is based on the 2,4,6 tri-iodinated benzene ring and provides the four major classifications of iodinated CT contrast agents; ionic monomer (top left), ionic dimer (top right), non-ionic monomer (bottom left), and non-ionic dimer (bottom right). For ionic contrast media, the carboxyl group (COOH) ionizes (COO^-) with sodium or meglumine to form anion and cation pairs. Side chains (R) vary but tend to be longer for non-ionic contrast.

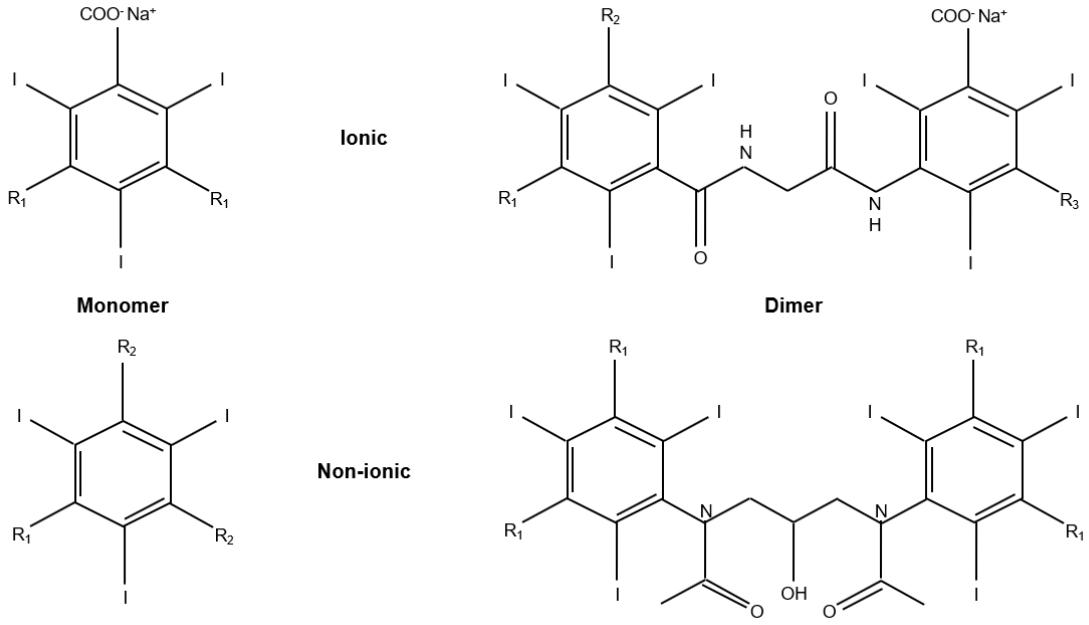


Figure 2: Schematic representation on log-log scales of the mass attenuation coefficient against x-ray energy. The iodine K-edge at 33keV demonstrates an abrupt increase in attenuation producing equivalent attenuation greater than lead and several orders of magnitude greater than bone and soft tissue. It should also be noted that within the range of 30-100 keV attenuation coefficients for biological tissues remains fairly uniform while the contrast agent (iodine) varies substantially (adapted from *15*).

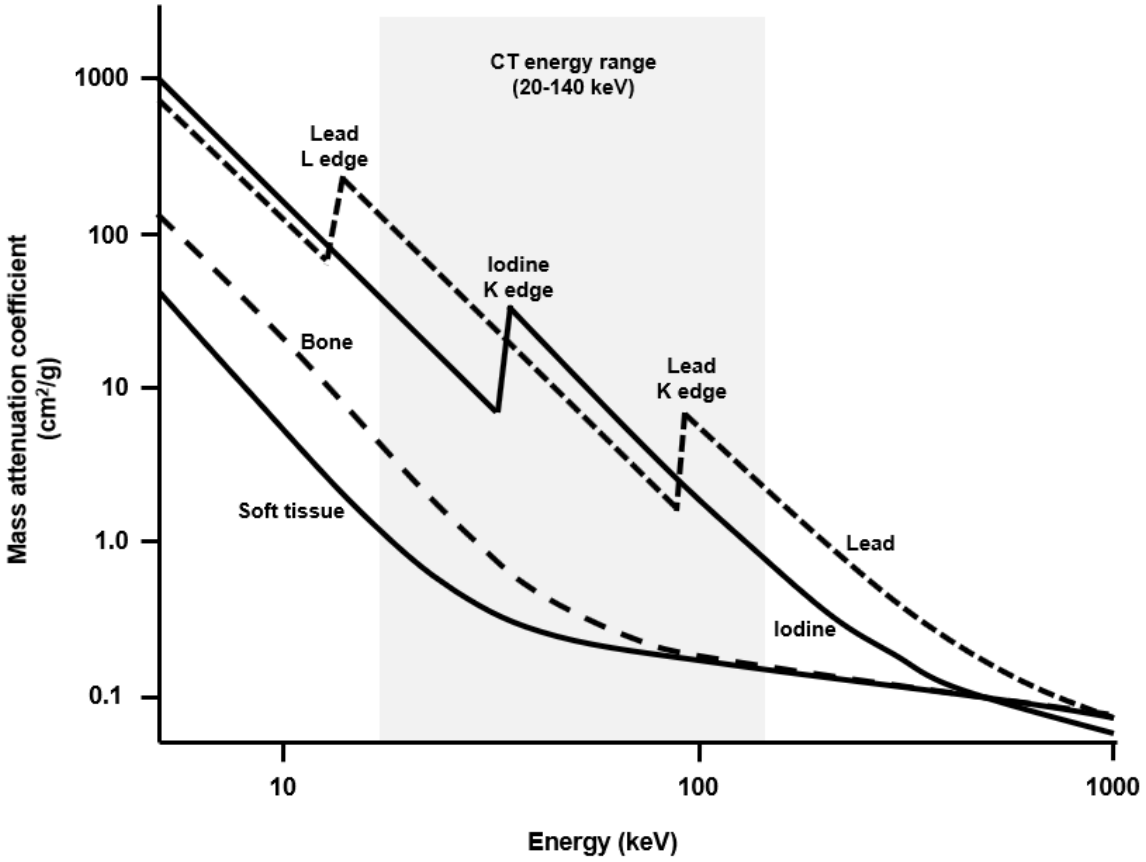


Figure 3: Modified two compartment model for iodinated CT contrast or gadolinium MRI contrast administered IV. The second extravascular compartment represents pathological tissue that may enhance with contrast administration and, therefore, be differentiated by surrounding normal tissue by a greater rate constant (k_5 over k_3 or k_4 over k_6). Refer to the previous article for more detailed interpretation of compartment models and rate constants (*2*).

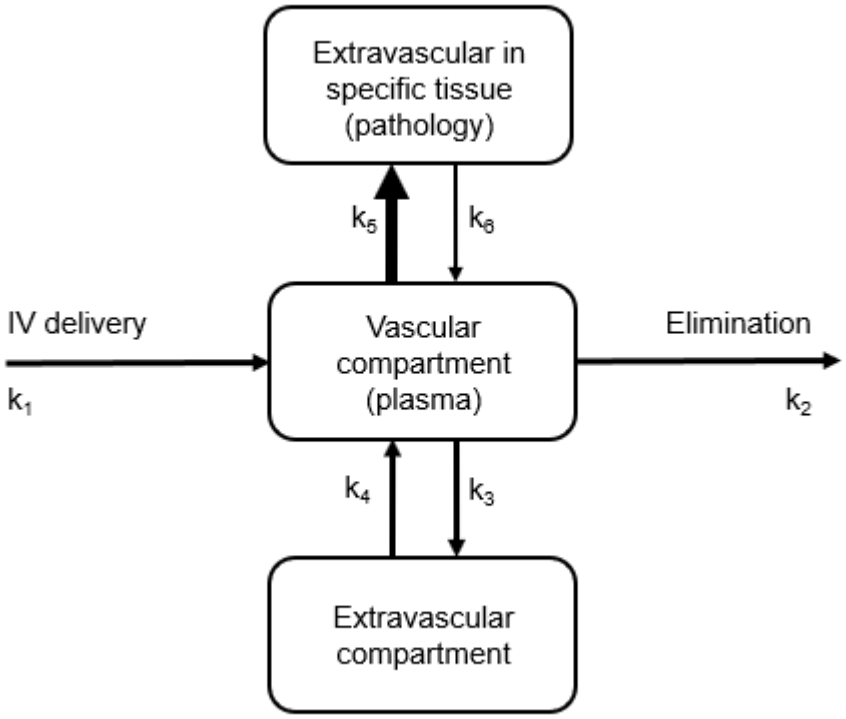


Figure 4: Flow chart of iodinated contrast reaction classification

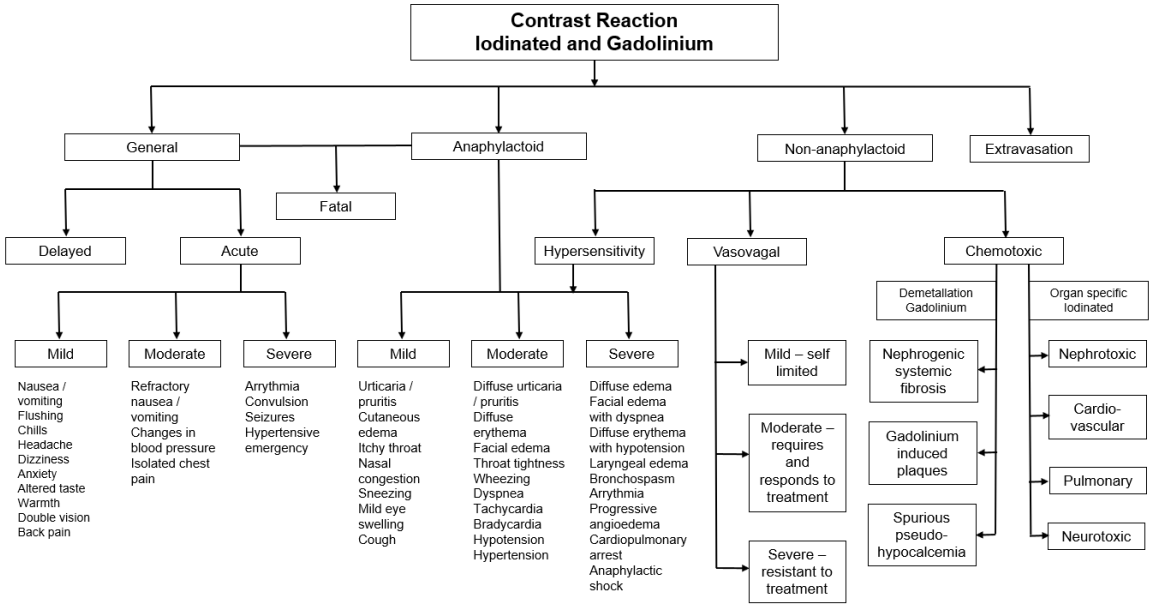


Figure 5: Flow chart outlining the interplay between factors contributing to the development of contrast induced nephrotoxicity. As outlined by bold boxes, vasoconstriction, oxidative stress, tubular cell damage and increased tubular pressure are the key drivers associated with cytotoxicity and viscosity as mediators.

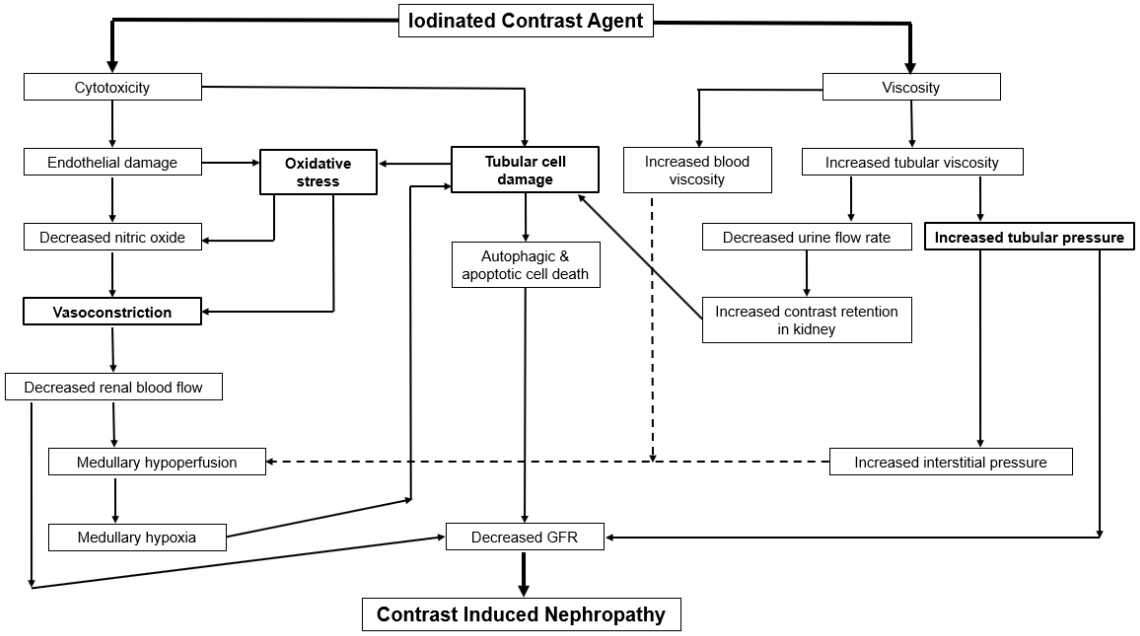
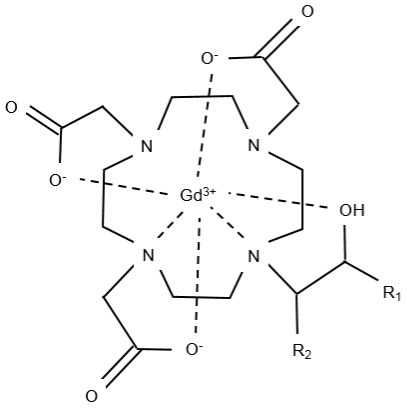


Figure 6: The chemical structure of gadolinium contrast agents adopts either a macrocyclic base (left) or a linear base (right) with the major differences between each agent being changes to the R groups.



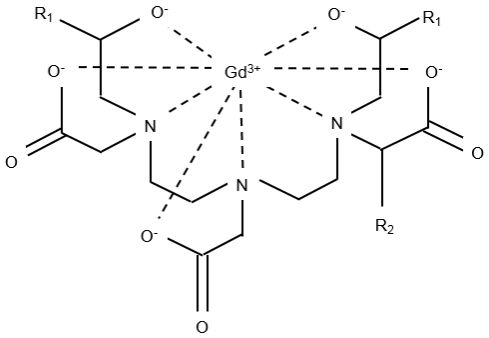


Figure 7: Schematic representation of the principle of T1 and T2 contrast enhancement in MRI. As represented at the bottom of the figure, hydrogen (protons) initially align with the magnetic field. A radiofrequency (RF) excitation pulse is applied to the proton which flips into the transverse plane. The RF pulse ends allowing the proton to relax back to the longitudinal plane. The T1 plot (top left) shows the effect of shortening the relaxation time with gadolinium contrast and resultant positive enhancement of the contrast. Likewise, the T2 plot (top right) shows the effect of shortening relaxation time with iron oxide contrast and resultant negative enhancement of the contrast.