Introduction

A universally accepted definition of Contrast-Induced Nephropathy (CIN) does not exist. The most commonly used definition for CIN in clinical trials is the elevation of serum creatinine by ≥0.5mg/dL or ≥25% occurring within 48 hours after administration of contrast media and the absence of an alternative etiology ***(Toprak, 2007a)***.

Increasing use of contrast media during radiological procedures has resulted in an increasing incidence of CIN, an iatrogenic disorder caused by exposure to contrast material ***(Pucelikova et al., 2008)***.

The incidence of CIN is reported to be 0.6% to 2.3% in a general population who do not have any risk marker for CIN ***(Toprak and Cirit, 2006a)***.

But incidence of CIN increase to 12-26% for those with renal disease or diabetes mellitus ***(Goldenberg and Matetzky, 2005)***.

The incidence of CIN requiring dialysis is approximately 0.4% and is associated with a 35.7% in-hospital mortality rate and has a 2-year survival rate of 18.2% ***(Tepel et al., 2006)***.

The strongly associated risk markers for CIN are preexisting renal failure, Diabetes Mellitus (DM), age greater than 70 years, concurrent use of nephrotoxic drugs, hyopvolemia, use of large amount of Contrast Medium (CM) or an ionic hyperosmolar CM, and congestive heart failure ***(Toprak and Cirit, 2006b)***.

Contrast agents are commonly used in diagnostic or interventional procedures, such as excretory urography, computerized tomography, coronary angiography and Magnetic Resonance Imaging (MRI), are becoming a great source of the iatrogenic acute renal failure known as CIN ***(Tepel et al., 2006)***.

The strategies for preventing CIN suggests that prophylactic N-acetylcysteine and hydration with sodium bicarbonate may be the best pharmacological approach to preventing CIN ***(Bareto, 2007)***.

Gadolinium-based MRI contrast agents were formerly considered as alternatives to X-ray-employed iodinated media. Recently, both renal and extra-renal toxicities have been reported following exposure to gadolinium in patients with underlying kidney disease ***(Perazella, 2007)***.

The administration of certain extracellular gadolinium based contrast media may trigger the development of Nephrogenic Systemic Fibrosis (NSF) in patients with severely reduced renal function (<30ml/min) or those on dialysis ***(Center for Disease Control and Prevention, 2007)***.

NSF, also known as Nephrogenic Fibrosing Dermopathy (NFD) has been described for the first time in renal transplant patients with poor transplant function in 1997 ***(Perazella, 2007)***.

On 7 February, 2007, the medical community was informed that gadodiamide is now not only contraindicated in patients with End-Stage Renal Disease (ESRD), but also in pre- or postoperative liver transplantation patients and due to their renal-organ immaturity, in newborns and infants up to 1 year old ***(Henning and Vedate, 2007)***.

Aim of the Essay

The aim of this essay is to highlight CIN as, the best definition, types of contrast media, pathophysiology, differential diagnosis, incidence and risk markers, most recent prevention strategies, prophylaxis, treatment. Lastly the strong association of gadolinium with NSF.

Definition of Contrast-Induced Nephropathy

The definition of contrast-induced nephropathy (CIN) is a major problem in clinical practice. According to the guidelines of European Society of Radiology, the term "contrast-induced nephropathy" indicates an impairment of renal function (the elevation of serum creatinine by ≥0.5mg/dl or ≥25%) occurring within 48 hours following the intravascular administration of contrast media and the absence of an alternative etiology ***(Morcos and Thomsen, 2003)***.

The Iohexok cooperative study defined CIN as an increase serum creatinine of ≥1mg/dl 48 to 72 hours post-contrast ***(Rudnick et al., 1995)***.

The Nephric Trials has two separate primary endpoints, including 0.5 and 1.0mg/dl rises in serum creatinine from day 0 to day 7 ***(Aspelin et al., 2003)***.

The definition, which requires smaller increases in serum creatinine (≥25%), is more sensitive for the diagnosis of CIN associated with clinically important adverse short- and long-term outcome ***(Weisbord et al., 2006)***. However, this definition should be restricted only

in patients who have increased baseline serum creatinine level of ≥1mg/dl ***(McCullough, 2006)***.

Serum cystatin C may detect CIN one to two days earlier than creatinine. Serum cystatin C has been proposed as an alternative endogenous marker of GFR, showing higher correlation to standard clearance methods such as inulin or iohexol clearance ***(Hojs et al., 2006)***.

The RIFLE (risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure) classification, which defines renal failure in terms of glomerular filtration rate or urine output, will be useful in the future to define CIN ***(McCullough et al., 2006)***.

In conclusion, a universally accepted definition of CIN does not exist. The most commonly used definition for CIN in clinical trial is the elevation of serum creatinine by ≥0.5mg/dl or ≥25% occurring within 48 hours after administration of contrast media and the absence of an alternative etiology ***(Toprak, 2007a)***.

The impairment tends to be non-oliguric and transient, with the peak serum creatinine usually occurring around day 3 and returning to normal in the majority of cases within 2 weeks ***(Waybill and Waybill, 2001)***.

Contrast Media

Types of contrast media:

Contrast media are in a base of either iodine or gadolinium and can be categorized by their osmlar and ionic properties ***(Kohtz and Thompson, 2007)***.

I. Iodinated contrast media:

Pharmacokinetics:

Iodinated contrast media are categorized according to their osmolarity, ionization and structure. Osmolarity refers to the concentration of particles in a solution and is expressed in osmoles of solute particles per liter of solution. Iodinated contrast media can be categorized according to their osmolarity to:

- High-osmolar contrast media: are 1.200 to 1.400mosm/L water; all of the available high-osmolar media are ionic.
- Low-osmolar contrast media: are 290 to 860mosm/L water; some are ionic some are nonionic.
- Iso-osmolar contrast media: is 275 to 285mosm/L water; only one product is available, and it is nonionic.

(Kimmie et al., 2007)

Contrast media that have high osmolarity pose a higher risk of CIN than those with low osmolarity. Because high-osmolarity agents are so much denser than human serum (the osmolarity of which is typically 275 to 285mosm/L water), they cause fluid to shift from the cells into the vascular compartment, upsetting renal homeostasis ***(Costa, 2004)***.

Iodinated contrast agents are also ionic or nonionic, depending on their atomic configuration. Nonionic contrast agents consist of three iodine anions (anions are ions with a negative electrical charge) and one neutral iodine atom; ionic contrast agents posses some combination of iodine anions and cations (cations are ions with a positive electrical charge). Iodine cations are though to be nephrotoxic ***(Bettmann, 2005)***.

Commercially available media are all tri-iodinated benzene derivatives and are classified according to their structure to monomeric and dimeric. In 1990s, agents with dimeric molecules containing two benzene rings were produced, which possessed the desirable qualities of no ionicity, low osmolarity combined with increased iodine atoms per molecule, and greater water solubility, but they were of a higher viscosity compared with their monomeric predecessors. The increased viscosity could potentially

affect renal blood flow and tubular urine flow ***(Katzberg, 1997)***.

Table (1) showing properties and comparison of commonly used iodinated radiocontrast media ***(Pucelikova et al., 2008)***.

Table (1): Properties and comparison of iodinated contrast media

Name (Trade Name)	Osmolarity	Ionicity
Diatrizoate (Gastrograffin)	High-osmolar	Ionic monomer
Iothalamate (Glofil)	High-osmolar	Ionic monomer
Ioxithalamate	High-osmolar	Ionic monomer
Ioxaglate (Hexabrix)	Low-osmolar	Ionic dimmer
Iohexol (Omnipaque)	Low-osmolar	nonionic dimmer
Iopamidol (Isovue)	Low-osmolar	nonionic dimmer
Ioversol (Optiray)	Low-osmolar	nonionic dimmer
Iopromide (Ultravist)	Low-osmolar	nonionic dimmer
Iobitridol	Low-osmolar	nonionic dimmer
Iomeprol	Low-osmolar	nonionic dimmer
Iodixanol (Visipaque)	Iso-osmolar	nonionic dimmer

The kinetics of distribution of all contrast media are similar, with low lipophilicity, low plasma protein binding and minimal biotransformation. The contrast particles quickly equilibrate across capillary membranes after intravenous injection. They tend to remain extracellular

with the exception of proximal renal tubular cells ***(Jakobsen et al., 1992)***.

Movement of particles back into the circulation occurs, resulting in a bi-exponential decay in plasma iodine levels, with an elimination half-time of about two hours ***(Morris and Fischer, 1986)***.

Nearly, all the injected substance is cleared by the kidney and excreted in the urine unchanged in those with normal renal function. However, hepatic metabolism, enterohepatic circulation and biliary elimination are increased in those with renal impairment ***(Bourin et al., 1997)***.

II. Gadolinium-containing contrast media:

Characteristics and pharmacokinetics:

Gadolinium (GD) is a paramagnetic rare earth-anoid metallic element with an atomic number of 64 and a molecular weight of 157 Dalton (Da). It has ferromagnetic properties (strongly attracted by a magnet). This quality makes it extremely useful as an intravenous/intra-arterial contrast agent for MRI/MRA to enhance images of various body organs and tissues. The trivalent gadolinium ion (Gd^{3+}) is very close to the divalent calcium ion as reflected

by size, bonding, coordination and donor atom preference ***(Evans, 1990)***.

As it is a metal, it must be an ionic form to be soluble in water and allow it to serve as an injectable contrast agent that will distribute throughout the body. However, gadolinium in this free ionic form (Gd^{3+}) is highly toxic and has been shown to precipitate in tissues (liver, lymph nodes, bones), obstruct calcium-ion passage through muscle cells and nerve tissue cells (reducing neuromuscular trans-mission), and interfere with intracellular enzymes and cell membranes by the process of transmetallation, a phenomenon whereby Gd^{3+} replaces endogenous metals such as zinc and copper ***(Bellin, 2006)***.

To prevent deleterious effects of Gd^{3+}, allow its use in humans, Gd^{3+} needs to be sequestered by non-toxic substances. This is achieved by binding Gd^{3+} to another agent, known generically as a "chelate". These chelates are large organic molecules that form a stable complex around the Gd^{3+}, do not readily dissociate in vivo, and thus serve to help make the ion biochemically inert ***(Lorusso et al., 2005)***.

These "Gd-chelates" can be classified into 4 main categories based on their biochemical structure (linear versus macrocyclic) and their charge (ionic versus

nonionic). Macrocyclic chelates hold Gd^{3+} more tightly than linear chelates, are more stable both in vitro and in vivo, and have lower dissociation rates ***(Runge, 2001)***.

The commonly employed Gd-chelates that are Food and Administration Drug (FDA) approved are noted in table (2) ***(Food and Drug Administration, 2007)***.

Table (2): FDA approved gadolinium contrast agents

Gadolinium formulation	Osmolarity (mosm/kg)	Charge	Molecular structure
Gadopentetate dimeglumine (Magnevist®)	1960	Ionic	Linear
Gadodiamide (Omniscan®)	650	Nonionic	Linear
Gadoteridol (Prohance®)	630	Nonionic	Cyclic
Gadobenate dimeglumine (MultiHance®)	1970	Ionic	Linear
Gadoversetamide (OptiMARK®)	1110	Nonionic	Linear

Most Gd-chelates posses a molecular weight of approximately 500Da. They have a wide range of plasma osmolarities (630mosm/L up to 1970mosm/L), which are importantly influenced by charge; nonionic Gd-chelates, such as gadoteridol and gadodiamide have plasma, osmolarities of 630 and 650mosom/L, respectively, while ionic agents such as gadopentetate dimeglumine and

gadoversetamide are extremely hyperosmolar (1960 and 1110mosm/L, respectively) ***(Bellin, 2006)***.

Following intravenous administration, Gd-chelates are rapidly distributed into the extracellular space, quickly reaching equilibrium between the plasma and interstitial compartments. They are restricted to the extracellular space and have limited protein binding; however, some Gd-chelates (gado-benate dimeglumine, gadoversetamide) also enter cells such as the hepatocyte ***(Lorusso et al., 2005)***.

Gd-chelates do not undergo biotransformation and are eliminated unchanged by the kidneys via glomerular filteration without any contribution from tubular secretion. Renal clearance of Gd-chelates range from 1.1 to 1.6ml/minute /kg in individuals with normal renal function (approximating the creatinine clearance). Over 95% of an injected dose is eliminated within 24 hours with <3% being eliminated in the faeces ***(Perazell and Rodby, 2007)***.

Moderate and severe kidney disease were also associated with increased mean Gd-chelate recovery in faeces (6% and 8%, respectively), suggesting increased faecal excretion in the setting of impaired kidney ***(Reinton et al., 1994)***.

In patients with more advanced (stage 5) chronic kidney disease (CKD), the pharmacokinetics of Gd-chelates is further impacted by the limited renal excretion. However, the relatively small molecular weight (500Da) and negligible protein binding make the Gd-chaltes ideal for removal with hemodialysis ***(Joffe et al., 1998)***.

About 97% of Gd is eliminated via the kidneys. Impaired renal function prolongs the half life of Gd from 1.96 hour in healthy persons to 5.61 hours and 9.18 hours in patients with stage 4 or 5 respectively of chronic kidney disease ***(Swan et al., 1999)***.

Hemodialysis removes Gd by more than 95% only after three dialysis sessions, while in patients undergoing peritoneal dialysis Gd is hardly removed ***(Saitoh et al., 2006)***.

Gadolinium-chelate nephrotoxicity:

Over the past 20 years of experience with the use of Gd-chelates for diagnostic imaging, these agents have come to be considered safe and well-tolerated. Adverse reactions to these agents include nausea, vomiting, headache, as well as pain and erythema at the injection sites due to thrombophlebitis. Anaphylactoid and allergic reactions, consisting of sweating, rash, itching and facial swelling are less common but nonetheless serious complications. The rate of minor reactions from gadolinium-based contrast media range from 1% to 4%, while serious reactions are extremely uncommon; both are relatively rare compared to what is typically reported for iodine containing contrast-media. While iodine containing contrast-media induced nephrotoxicity is well described and common, the issue of Gd-chelate induced nephrotoxicity is highly controversial ***(Perazella and rodby, 2007)***.

Since Gd-chelates have characteristics similar to iodinated radiocontrast, including hyperosmolarity and renal clearance entirely dependent upon glomerular filtration, nephrotoxicity was an obvious concern. Early studies in normal subjects as well as small groups of patients with mild to moderate levels of underlying kidney dysfunction suggested a favorable renal safety profile ***(Niendorf et al., 1993)***.