Extracellular Water Soluble Contrast Media (CM); an overview

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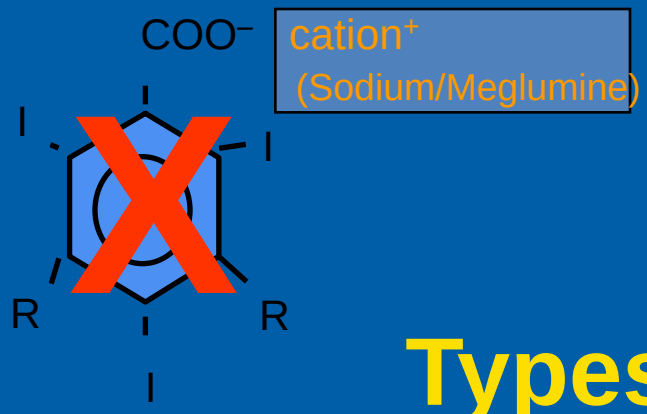
Extracellular Water Soluble Contrast Media (CM)

- Iodine based (ICM)
- Gadolinium based CM (Gd-CM)

- Types of ICM and Gd-CM
- Pharmacokinetics
- Important physicochemical features that influence the safety of CM
  - ICM
    - Osmolality
    - Ionicity
    - Viscosity
  - Gd-CM
    - Shape of the molecule (linear, macrocyclic)
    - Ionicity
    - Osmolality

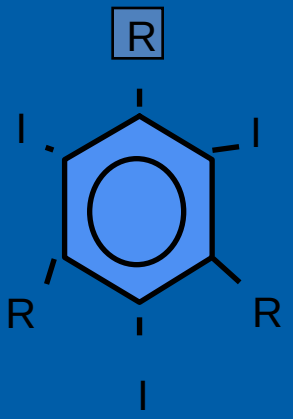
- Classifications of CM reactions
- Important Information to be obtained before CM injection

Types of ICM



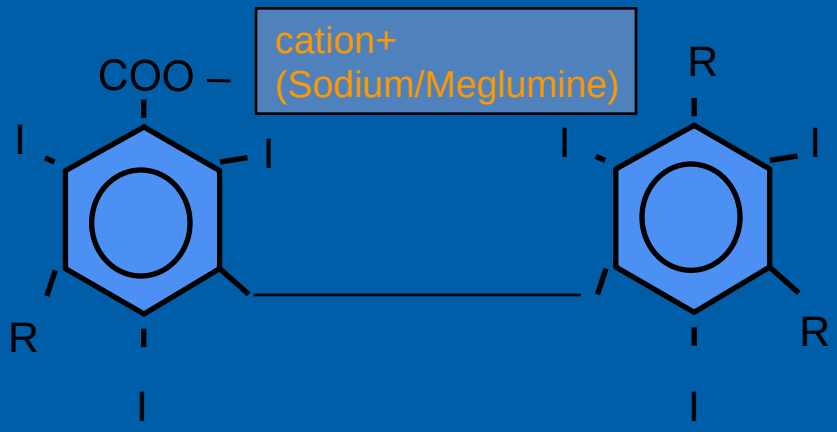
Ionic monomer

(3 iodine atoms : 2 particles, Ratio : 1.5)



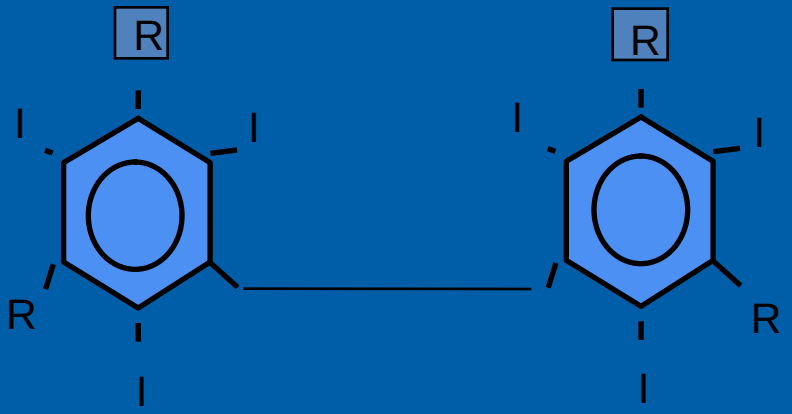
Non-Ionic monomer

(3 iodine atoms :1 particle, Ratio : 3.0)



Ionic dimer

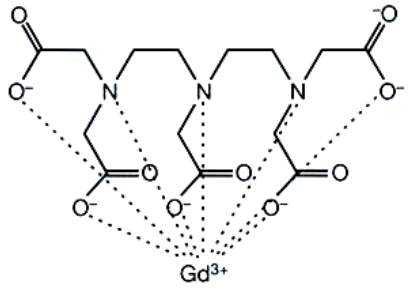
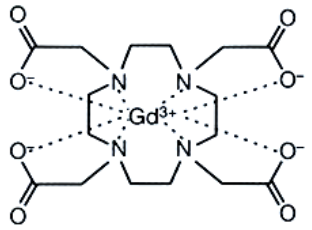
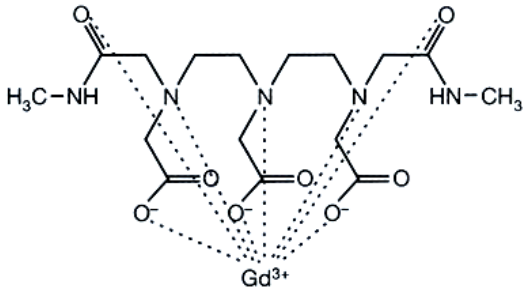
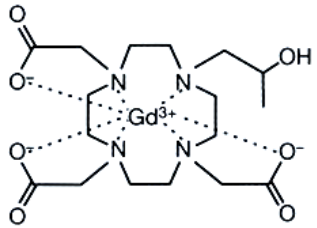
(6 iodine atoms : 2 particles, Ratio : 3.0)



Non-Ionic dimer

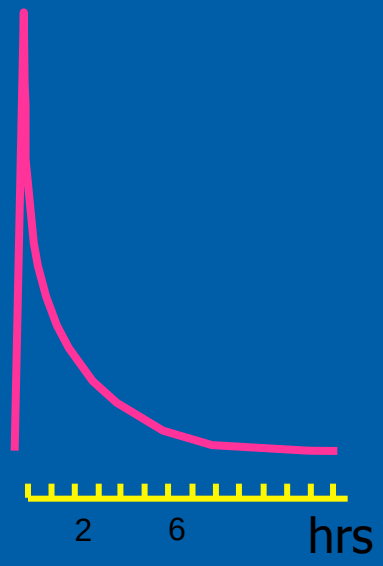
(6 iodine atoms :1 particle, Ratio : 6.0)

Types of Gd-CM

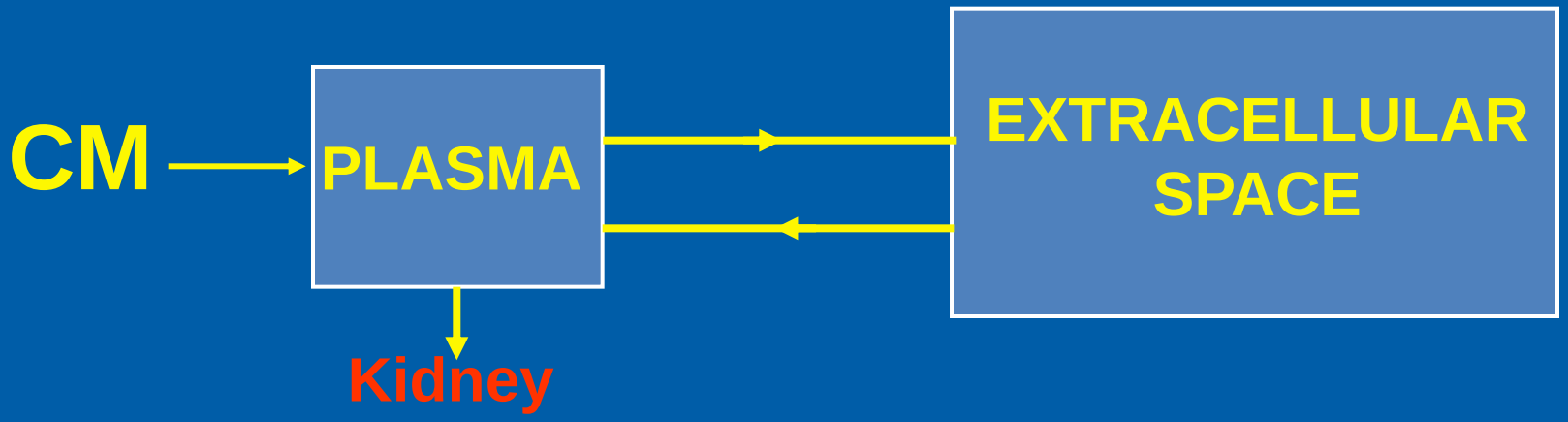
	linear	Cyclic
Ionic	a)  Gd-DTPA Ionisk lineært Gd kompleks	b)  Gd-DOTA Ionisk makrocyklisk Gd kompleks
Non-ionic	c)  Gd-DTPA-BMA Non-ionisk lineært Gd kompleks	d)  GdHP-DO3A Non-ionisk makrocyklisk Gd kompleks

Pharmacokinetics (Intravenous injection)

After intravenous injection of contrast medium 70% of the injected dose disappears from plasma to extravascular interstitial space within 2-5 minutes



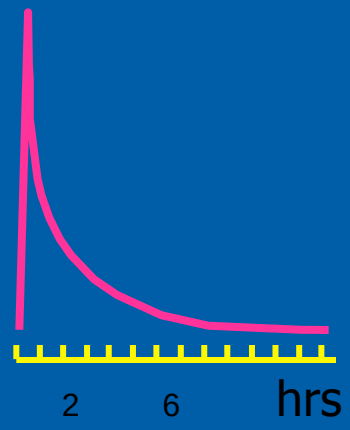
Pharmacokinetics (Intravenous injection)



- Contrast Medium diffuse from plasma to extravascular space
- Reverse diffusion also takes place
- Complete equilibration occurs about 2 hours after injection
- Contrast medium filtered through glomeruli all the time

Pharmacokinetics (Intravenous injection)

- 2 hours 50% excreted in urine
- 4 hours 75% excreted in urine
- 24 hours 95% excreted in urine
- Less than 2% is excreted via the biliary system

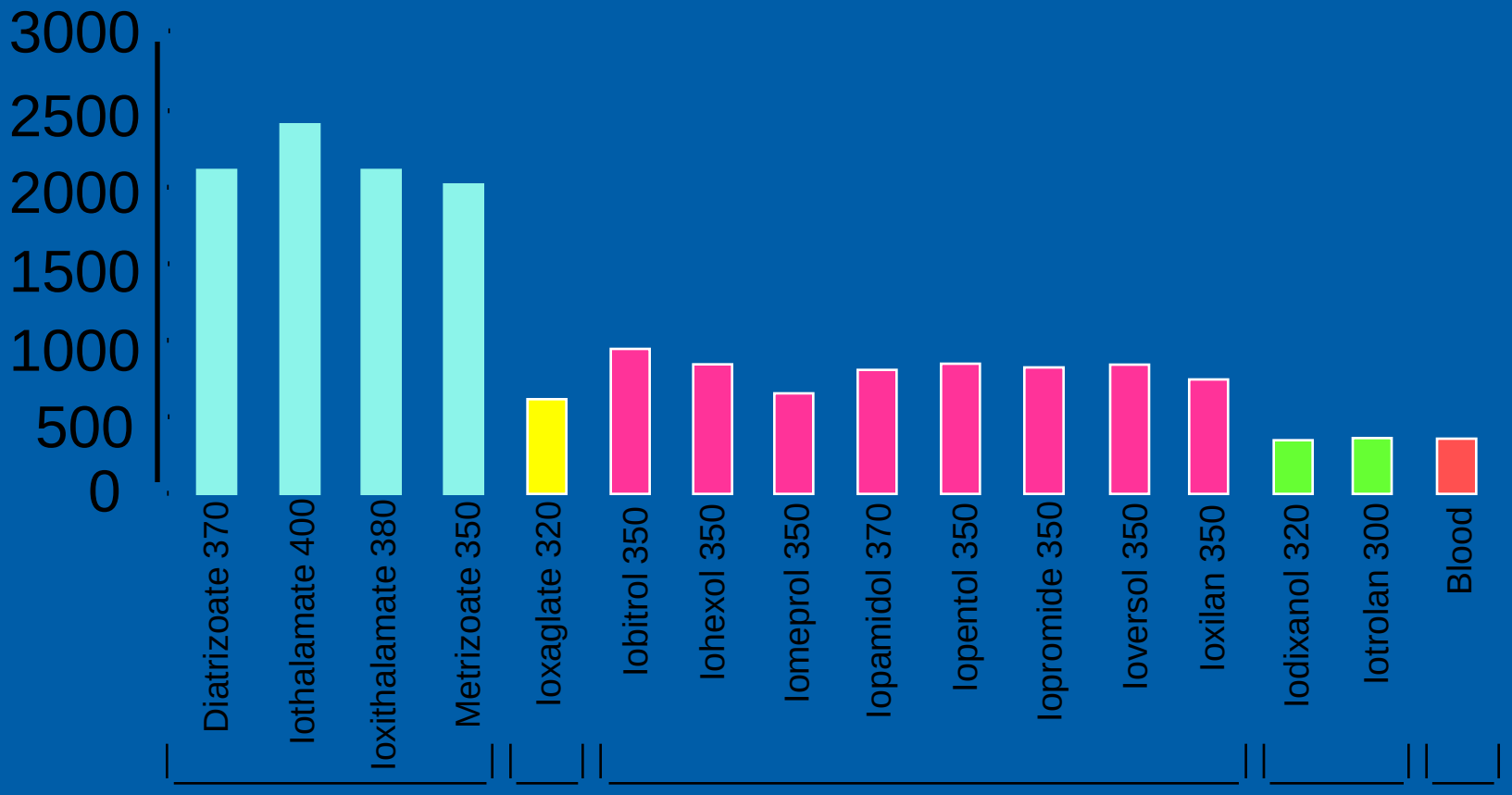


- Minor intracellular penetration
- Do not cross intact blood - brain barrier
- Not metabolised

Important physicochemical features that influence the safety of ICM

- Osmolality (mosmol/Kg H_2O)
- Viscosity (CP at 37°)
- Ionicity

Osmolality (mOsm/kg water) at 37°C of currently available iodinated contrast media



Osmotoxicity

Shift of fluids from the intracellular to extracellular space

↓

Cell dehydration and increase intracellular fluid viscosity

↓

Adverse effects on cellular function

Osmotoxicity

- Vascular pain
- Endothelial damage
- Thrombophlebitis
- Bradycardia in cardioangiography
- Increase pulmonary arterial pressure in patients with pulmonary hypertension
- Contributes to the nephrotoxicity of CM

Viscosity

- High viscosity may cause
  - Difficulty in high flow injection
  - Reduce blood flow in microcirculation
  - Increase urine viscosity which could be a factor in the pathophysiology of contrast nephrotoxicity

Ionicity

- Carboxyl group Increases the cytotoxicity
- Ion toxicity (sodium ions; neurotoxicity, cardiotoxicity)
- Ionic CM are more vasoactive than non-ionic agents

Important physicochemical features that influence the safety of Gd-CM

- Ionicity
- Osmolality
  - Not crucial as the volume of Gd-CM injected is small (<20ml) in most applications
- Shape of the molecule (linear, macrocyclic)
  - The most important safety aspect of Gd-CM particularly in patients with reduced renal function

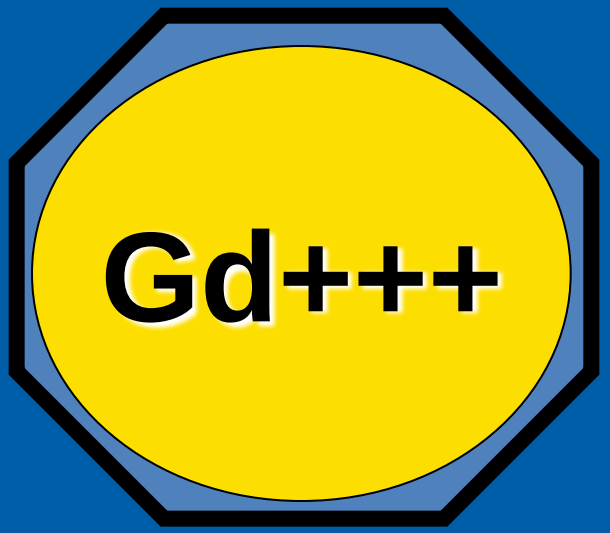
Factors which determine the stability of Gd-CM

- **Shape:** linear or cyclic
  - Macrocyclic chelate offers a better protection and binding to Gd+++ in comparison to the linear structure

Morcos SK, Br J Radiol, 2007; 80: 73-76

Macrocyclic chelate is more stable than the linear chelate

- Macrocyclic
  - Pre-organised
  - Rigid ring
  - Near optimal size to cage Gd^{+++}

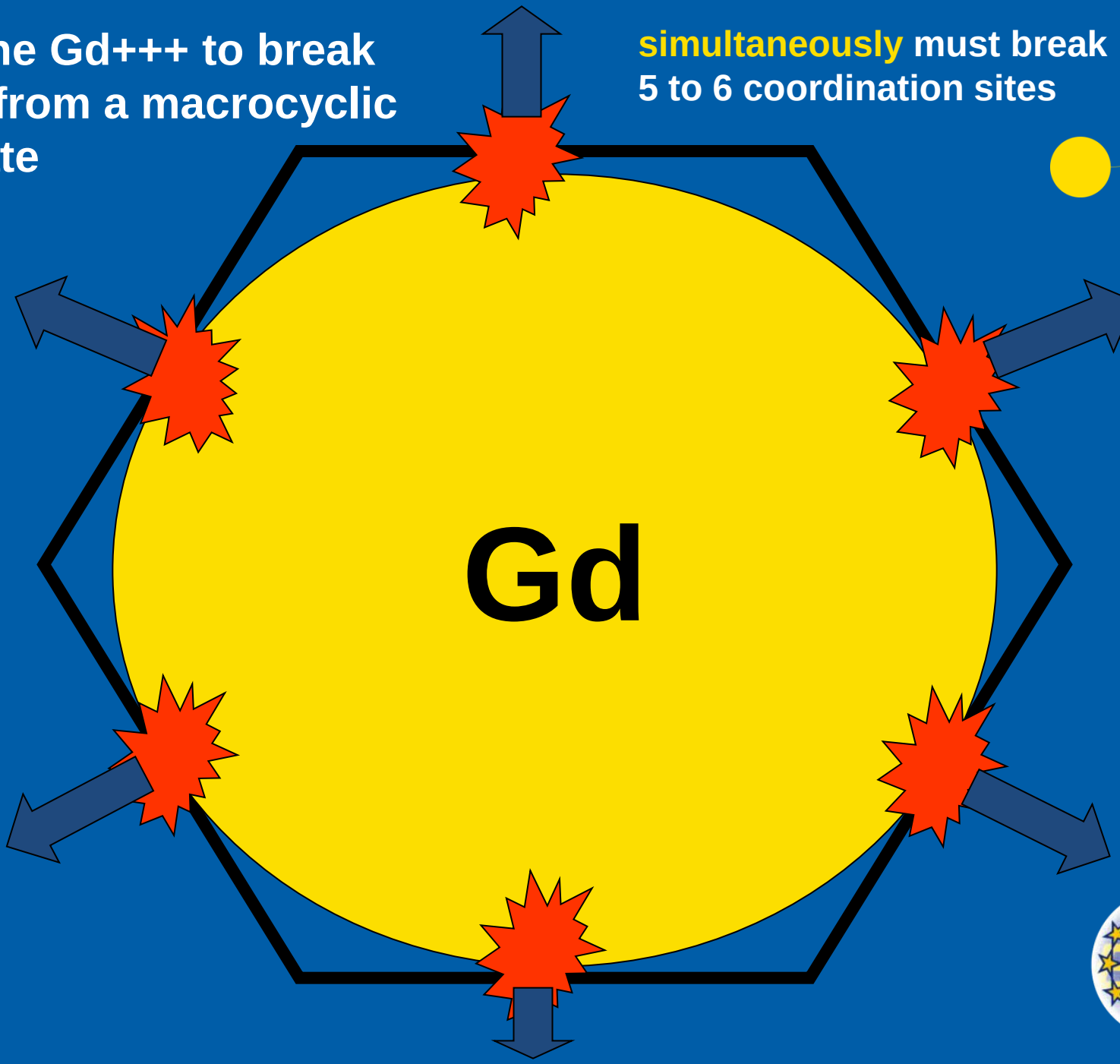


A rigid cage which strongly holds Gd within its cavity

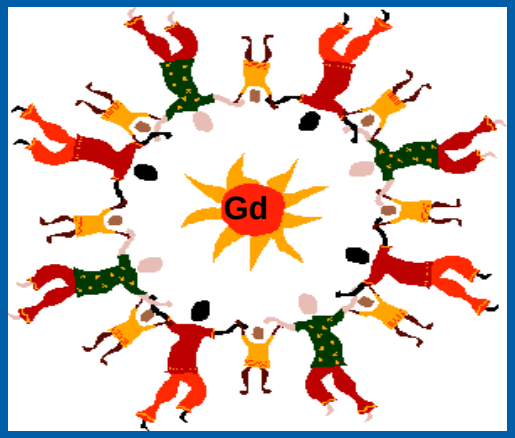
MACROCYCLIC CHELATE

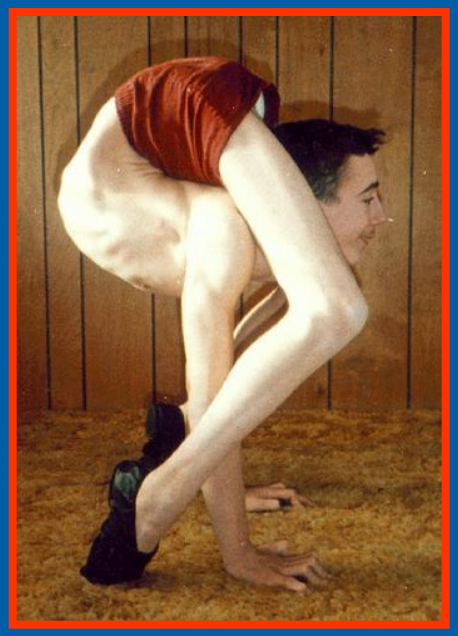
For the Gd+++ to break free from a macrocyclic chelate

simultaneously must break 5 to 6 coordination sites



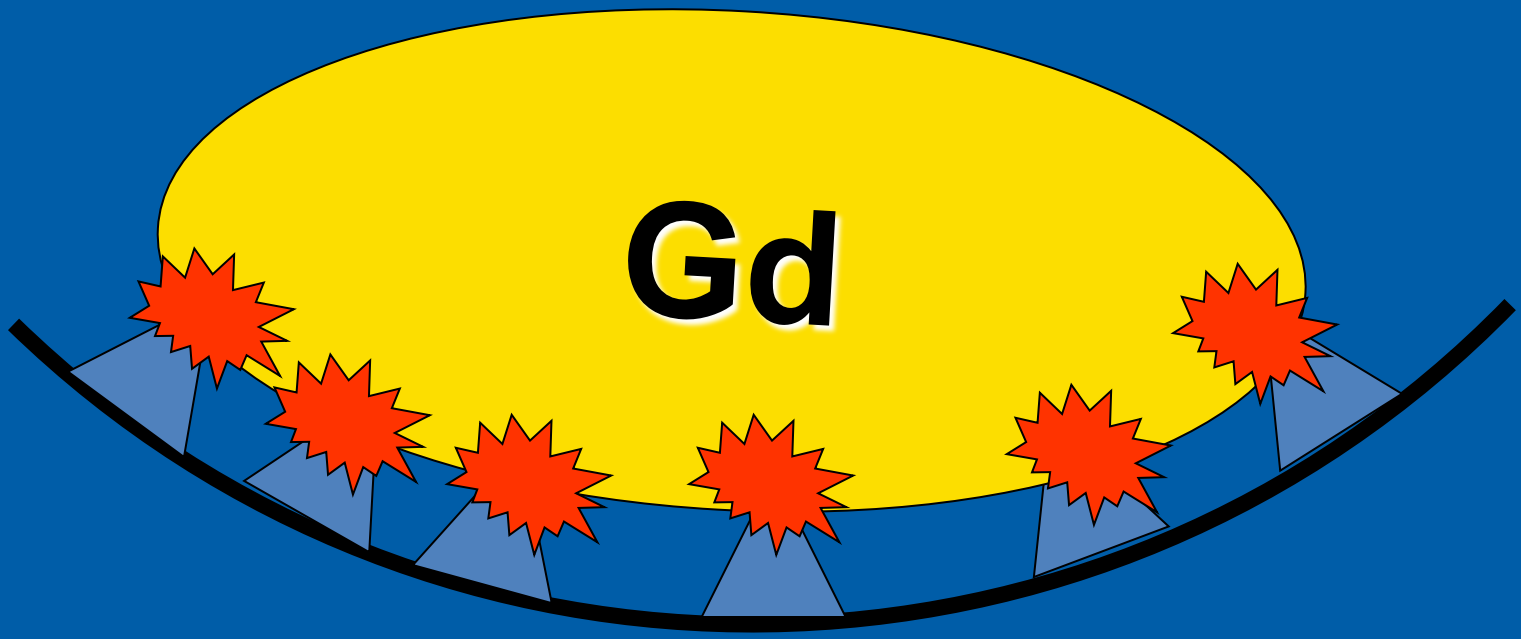
Macrocyclic chelate is more stable than the linear chelate



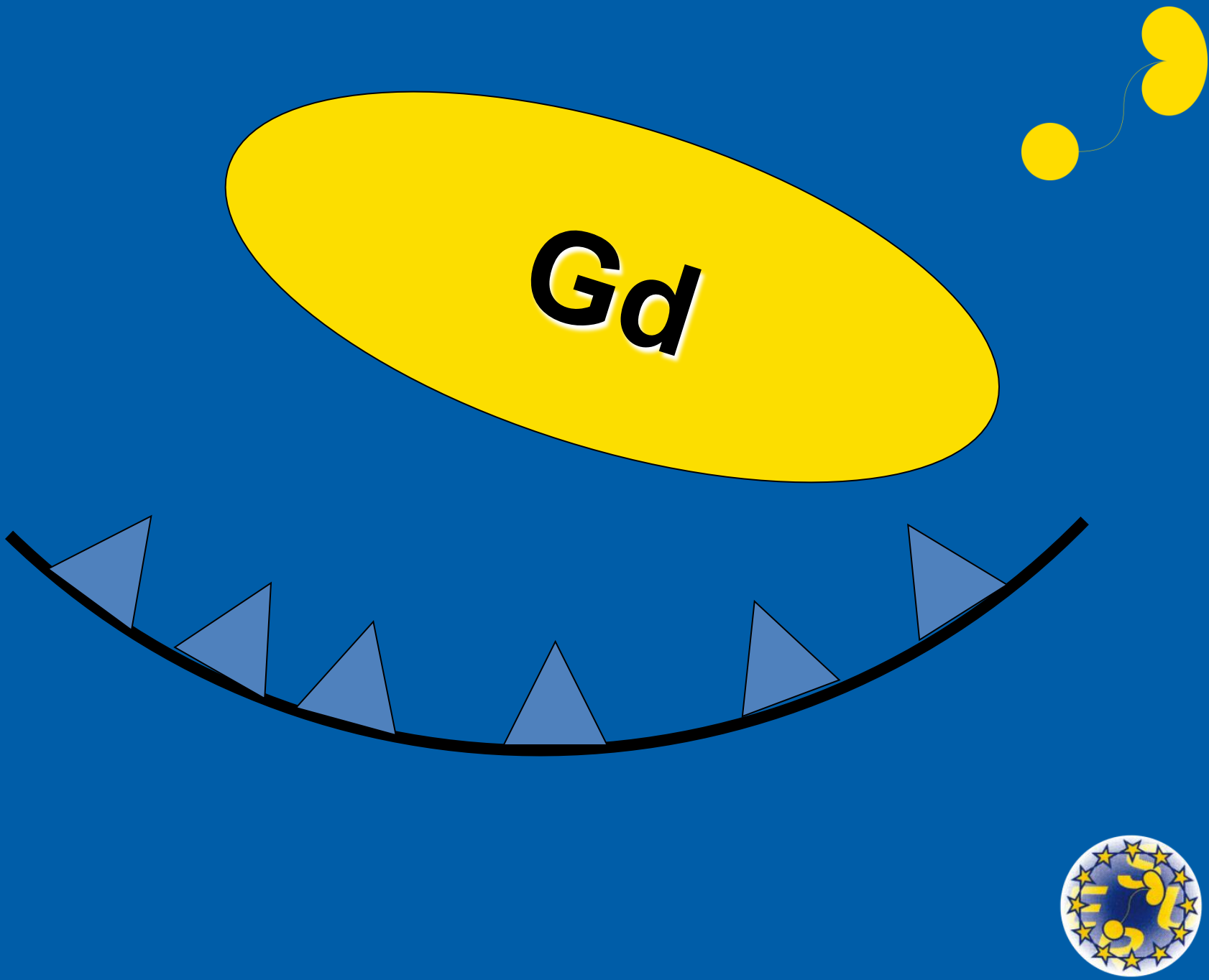


- Linear
  - Open chains
  - Not pre-organised
  - Flexible
  - Fold and unfold easily

Gd can break free easily from the linear chelate as the separation occurs **sequentially**



Gibby WA et al, Invest Radiol 2004; 39: 138-142

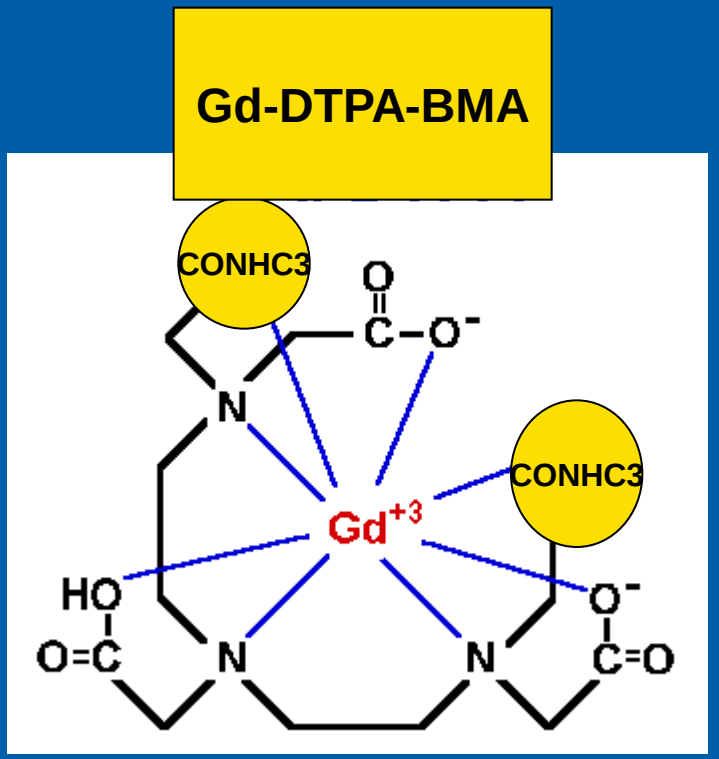

Gd

Factors which determine the stability of Gd-CM

- **Ionicity:** ***ionic or non-ionic***
  - **Non-ionic chelates are less stable than ionic ones**
    - Replacement of a carboxyl group by a non ionic group weaken the grip of the chelate to Gd+++ particularly in the non ionic linear molecule

Morcos SK, Br J Radiol, 2007; 80: 73-76

- In the non-ionic linear chelate the carboxyl groups are reduced to 3 as the other two carboxyl groups have been replaced by non ionic methyl amide
- The amide has a weaker binding to Gd^{+++} in comparison to the negatively charged carboxyl groups
- Decrease the grip of the chelate on the Gd atom



Markers of GD-CM stability *in vitro* assessment

- Thermodynamic stability (at high pH ~11)
- Conditional stability (thermodynamic stability at pH7.4)
- Dissociation half life at pH 1.0
- ***The higher the value the higher the stability of the chelate***
- Excess chelate
- ***Presence of a large amount of excess chelate in the commercial preparation is an indirect marker of the instability of the molecule***

Morcos SK, Br J Radiol, 2007; 80: 73-76

Extracellular Gd-CM	Type	Thermo-dynamic stability constant	Condition stability	Excess chelate (mg/ml)	Dissociation half-life at pH 1.0
Gadoversetamide (OptiMark)	Non-ionic linear	16.6	15	28.4	Not available
Gadodiamide (Omniscan)	Non-ionic linear	16.9	14.9	12	35 sec
Gadopentetate (Magnevist)	Ionic linear	22.1	18.1	0.4	10 min
Gadobenate (MultiHance)	Ionic linear	22.6	18.4	None	Not available
Gadobutrol (Gadovist)	Non-ionic cyclic	21.8	15.5	Not available	18h*
Gadoteridol (ProHance)	Non-ionic cyclic	23.8	17.1	0.23	4h*
Gadoterate (Dotarem)	Ionic cyclic	25.8	18.8	None	85h*

*** pH=1.2, 37˚C Port Br J Radiol 2008; 81: 258-259**

- Classifications of CM reactions
  - Acute non renal
    - Mild
    - Moderate
    - Severe

- Classifications of CM reactions
  - Renal (CIN)
    - Develop in patients with risk factors particularly pre-existing renal impairment in association with DM

- Classifications of CM reactions
  - Delayed
    - Skin reactions (ICM)
    - Thyrotoxicosis (ICM)
    - NSF (Gd-CM)

Important Information before CM Injection

It is crucial to identify high-risk patients

BEFORE

CM administration

ESUR Questionnaire Before CM Administration

- It is vital that all the relevant information about the patient is readily available before CM administration to minimize the potential risks and to take the necessary measures to prevent an adverse reaction.
- It should be completed by the referring physician **when** the examination is requested

- An awareness of the drug history is also important as there is the possibility of interaction between CM and other drugs.

- In emergency situations the radiologist should try to obtain as many of the questionnaire answers as possible before CM administration and make a judgment of benefit against risk depending on the clinical problem under investigation.

- Demanding an extensive list of information with the request is not practical and may not receive the cooperation of referring clinicians.

- Thus, it is important to focus the questionnaire on important risk factors for serious complications that are most likely to be encountered in clinical practice.

- The proposed CM questionnaire should be considered as a supplement to the standard referral for imaging examinations.

- The completed contrast medium questionnaire should be forwarded together with the request to the Imaging Department for further action.

ESUR Questionnaire before ICM administration

1. History of moderate or severe reaction to an iodinated contrast medium □ Yes □ No
2. History of allergy requiring treatment □ Yes □ No
3. History of asthma □ Yes □ No
4. Hyperthyroidism □ Yes □ No
5. Heart Failure □ Yes □ No

6.	Diabetes Mellitus	□ Yes □ No
7.	History of renal disease	□ Yes □ No
8.	Previous renal surgery	□ Yes □ No
9.	History of proteinuria	□ Yes □ No
10.	Hypertension	□ Yes □ No
11.	Gout	□ Yes □ No

12. Most recent measurement of serum creatinine

Value……

Date ……

13. Is the patient currently taking any of the following drugs

Metformin for treatment of diabetes	□ Yes □ No
Interleukin 2	□ Yes □ No
NSAIDs	□ Yes □ No
Aminoglycosides	□ Yes □ No
β-blockers	□ Yes □ No

Completed by _____ Date _____

ESUR Questionnaire before Gd-CM administration

1. History of moderate or severe reaction to a MRI contrast medium
   □ Yes □ No
2. History of allergy requiring treatment □ Yes □ No
3. History of asthma □ Yes □ No
4. Has the patient end-stage renal failure (eGFR < 30 ml/min/1.73m^2) or is the patient on dialysis
   □ Yes □ No

1. History of hemosiderosis or hemochromatosis □ Yes □ No
2. Previous reaction to dextran □ Yes □ No

Completed by _____Date_____

Recommendation

- Include the questionnaire in your Radiology Information System (RIS).
- No referrals without a filled-out questionnaire.