Extracellular Water Soluble Contrast Media (CM); an overview

Professor S K Morcos
Consultant Radiologist

University of Sheffield

Sheffield Teaching hospitals
NHS Trust
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

Ionic

Linear

Gd-DTPA
Ionisk lineært Gd kompleks

Gd-DOTA
Ionisk makrocyklisk Gd kompleks

Non-ionic

Gd-DTPA-BMA
Non-ionisk lineært Gd kompleks

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.

![Graph showing the decline of contrast medium concentration over time with labels for 2 and 6 hours on the x-axis labeled as 'hrs'.]
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 H₂O)
- Viscosity (CP at 37°)
- Ionicity
Osmolality (mOsm/kg water) at 37°C of currently available iodinated contrast media

- Diatrizoate 370
- Iothalamate 400
- Ioxithalamate 380
- Metrizoate 350
- Ioxaglate 320
- Iobitrol 350
- Iohexol 350
- Iomeprrol 350
- Iopamidol 370
- Iopentol 350
- Iopromide 350
- Ioversol 350
- Ioxilan 350
- Iodixanol 320
- Iotrolan 300
- Blood
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

$$\text{Gd}^{+++}$$
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.

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 pH 7.4)
- 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
<table>
<thead>
<tr>
<th>Extracellular Gd-CM</th>
<th>Type</th>
<th>Thermo-dynamic stability constant</th>
<th>Condition stability</th>
<th>Excess chelate (mg/ml)</th>
<th>Dissociation half-life at pH 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadoversetamide (OptiMark)</td>
<td>Non-ionic linear</td>
<td>16.6</td>
<td>15</td>
<td>28.4</td>
<td>Not available</td>
</tr>
<tr>
<td>Gadodiamide (Omniscan)</td>
<td>Non-ionic linear</td>
<td>16.9</td>
<td>14.9</td>
<td>12</td>
<td>35 sec</td>
</tr>
<tr>
<td>Gadopentetate (Magnevist)</td>
<td>Ionic linear</td>
<td>22.1</td>
<td>18.1</td>
<td>0.4</td>
<td>10 min</td>
</tr>
<tr>
<td>Gadobenate (MultiHance)</td>
<td>Ionic linear</td>
<td>22.6</td>
<td>18.4</td>
<td>None</td>
<td>Not available</td>
</tr>
<tr>
<td>Gadobutrol (Gadovist)</td>
<td>Non-ionic cyclic</td>
<td>21.8</td>
<td>15.5</td>
<td>Not available</td>
<td>18h*</td>
</tr>
<tr>
<td>Gadoteridol (ProHance)</td>
<td>Non-ionic cyclic</td>
<td>23.8</td>
<td>17.1</td>
<td>0.23</td>
<td>4h*</td>
</tr>
<tr>
<td>Gadoterate (Dotarem)</td>
<td>Ionic cyclic</td>
<td>25.8</td>
<td>18.8</td>
<td>None</td>
<td>85h*</td>
</tr>
</tbody>
</table>

* 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
<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.</td>
<td>Diabetes Mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>History of renal disease</td>
<td></td>
<td></td>
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<tr>
<td>8.</td>
<td>Previous renal surgery</td>
<td></td>
<td></td>
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<tr>
<td>9.</td>
<td>History of proteinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Gout</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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/1.73m²) 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.