Contrast agent for Imaging: *from a molecule to a contrast media for clinical applications*

*Federico Sabino, MD*

*Sofia, June 2-2017*
Summary

• **Overview of the development process**
  – Key milestones: from the lab to the clinics

• **Flags on key scientific evidences**
  – Finished product
  – Efficacy
  – Safety
  – Special case

• **conclusions**
The R & D process of a new drug

**Discovery**
- Exploratory & Identification
- Pre-clinical / toxicology-pharmacology-kinetics

**Development**
- Clinical Phase I
- Phase II - III
- Approval

**Pharmacovigilance**

**Market**

**Stop/Go decision at any time**

**GMP production**
1. Raw material production & analysis
2. Formulation & analysis, stability

**Scale up**

New indications
The R & D process of a new drug

Key questions:
is it **safe**, **effective** and has it **any competitive advantages**?

case of **Iomeprol**, a contrast agent for X-Ray

Evidences
Contrast Media-CM

1. CM refers to the solvent water together with all the solutes such as
   ▪ Iodinated chemical compounds and
   ▪ various ions and other additives.

2. The iodinated compounds may either be
   ▪ ionic (contrast agent salts)
   ▪ or nonionic (contrast agent molecules).
   ▪ Nonionic CM may be formulated with a minor ionic additive/supplement.

   The terms ion(s) and ionic have been used for all ion-related matters and not the term electrolyte(s), which is largely synonymous.
CM are not a homogeneous category of drugs for diagnostic use

• differ from each other in
  – physical and chemical characteristics (osmolality, viscosity, chemo-intrinsic toxicity, concentration)
  – electrolyte content, excipients, additives (EDTA) and other stabilizers in solution
  – with different effects on the Heart, Brain, Kidney and Thyroid

able to influence the efficacy and tolerability (hypersensitivity, potential adverse events - renal / heart / brain & thyroid)
Non ionic x-ray contrast agents: general features

**Ideal properties**
- Water solubility
- Chemical and heat stability
- Biologically inert (nonantigenic)
- Low viscosity
- Low osmolality
- Selective excretion (i.e. kidney)

**Safety**
- Cost

**Finished product features**
- High stability (up to 400 gI/ml)
  - Minimum presence of additives
  - Longest shelf life
- Low viscosity
- Low osmolality
- Low neurotoxicity
- Low nephrotoxicity

**Iomeron** (Bracco 1979)
EDTA effects

In normal plasma Ca-ion is in equilibrium with Ca bound to proteins: the presence of EDTA may alter this balance


2. Heart: negative inotropic effect in patients with severe CAD (up to the electromechanical dissociation), for alterations the ratio Ca ++ / Na ++ in the myocardium (Caulfield BJ et al, Circulation 1975; Baltaxe InvRadiol 1976; Higgins Circulation 1978)

3. Thyroid: due to the free iodide which can be released from CM (Wang J.Pharm Sci 1980;69:671-5). To manage it you add EDTA which alters the relationship Ca ++ / Na ++


<table>
<thead>
<tr>
<th>lomeron</th>
<th>iopamiro</th>
<th>Xenetix</th>
<th>Visipaque</th>
<th>Ultravist</th>
<th>Omnipaque</th>
<th>Optiray</th>
</tr>
</thead>
<tbody>
<tr>
<td>lomeprol</td>
<td>lopamidol</td>
<td>lobarbital</td>
<td>iodixanol</td>
<td>lopromide</td>
<td>lohexol</td>
<td>loversol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EDTA</th>
<th>Commitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>SPC</td>
<td>SPC</td>
</tr>
</tbody>
</table>
Heart Rate Disorders


• **Arrhythmias** represent the 2nd cause of adverse events following interventional procedures.

• Those related to the CM depend on:
  – Direct action on the cell membrane, and, partially on reflected ones
  – Osmolarity
  – Viscosity
  – Ca-subtractive activity.

  *Some formulations require the presence of EDTA.*

• They are different, depending on the used CM
### Chemical and physical characteristics of some iodinated contrast media

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ionic</strong></td>
<td><strong>Non-Ionic</strong></td>
</tr>
<tr>
<td><strong>Compound</strong></td>
<td>Osmolality mOsm/kg H₂O</td>
</tr>
<tr>
<td>Diodrast</td>
<td>1515</td>
</tr>
<tr>
<td>Iothalamate</td>
<td>1843</td>
</tr>
<tr>
<td>Ioxitalamate</td>
<td>2130</td>
</tr>
<tr>
<td>Ioxaglate</td>
<td>600</td>
</tr>
<tr>
<td><strong>Dimer</strong></td>
<td><strong>Compound</strong></td>
</tr>
<tr>
<td>Iohexol</td>
<td>672</td>
</tr>
<tr>
<td>Iopentol</td>
<td>810</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>630</td>
</tr>
<tr>
<td>Ioversol</td>
<td>645</td>
</tr>
<tr>
<td>Iopromide</td>
<td>610</td>
</tr>
<tr>
<td>Iomeprol</td>
<td>520</td>
</tr>
<tr>
<td>Iobitridol</td>
<td>695</td>
</tr>
<tr>
<td>Ioxilan</td>
<td>585</td>
</tr>
<tr>
<td>Iotrolan</td>
<td>320</td>
</tr>
<tr>
<td>Iodixanol</td>
<td>290</td>
</tr>
</tbody>
</table>
The plasma profiles is well described by a two compartment model.

- The $\alpha$ phase (distribution) is characterized by an average half-life of 22 min.
- The $\beta$ phase (elimination) by an average half-life of 1.8 hours.
IOMERON – i.v. administration – plasma kinetics

Dose: 1.6g(I)/kg

<table>
<thead>
<tr>
<th></th>
<th>$t_{1/2,\alpha}$ h</th>
<th>$t_{1/2,\beta}$ h</th>
<th>$V_c$ L/kg</th>
<th>$V_\beta$ L/kg</th>
<th>$Cl_{\text{tot}}$ L/(h*kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.18</td>
<td>1.68</td>
<td>0.16</td>
<td>0.26</td>
<td>0.10</td>
</tr>
<tr>
<td>s.d.</td>
<td>0.09</td>
<td>0.24</td>
<td>0.03</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Rapidly eliminated from the plasma compartment

Distributed into the plasma and the interstitial fluid

Glomerular filtration is the primary elimination mechanism

No difference in the mean pk parameters are detected among the different dose levels.

DOSE INDEPENDENT KINETICS
Plasma level decay of iomeprol

- Healthy Subjects
- Mild renal impairment
- Moderate renal impairment
- Severe renal impairment

mg (iomeprol)/mL vs hours
Most of the iodine dose (approximately 90%) is recovered in the urine during a 24- and 96 hour interval.

Essentially all of the iodinated material excreted into urine following lomeprol treatment corresponded to unchanged lomeprol.

1. Lomeprol do not undergo appreciable metabolism or deiodination.

2. No alteration in elimination kinetics on passage through the kidneys.

3. The drug is essentially cleared through the kidney.
IOMERON – PK in special population

Renal impairment

- **mild and moderate:** little effect on the final total recovery of iomeprol
- **severe renal impairment:** considerable effect

Progressive decreases in both the $\text{CL}_{\text{tot}}$ and $\text{CL}_{\text{ren}}$ of iomeprol and progressive increases in plasma $t_{1/2\beta}$ are observed with increasing degrees of renal impairment.

Paediatric subjects
Pharmacokinetic profile of **iomeprol** is similar to the profile in adults.
IOMERON – i.t. administration – plasma kinetics

It is possible to construct a 3 compartment model with an absorption phase, and 2 elimination phases (CSF/plasma/tissue).

Three different doses:
8 -10 – 12 mL of 300 mg(I)/mL

1. $C_{\text{max}}$ level is reached 2 hours after administration.
2. half-life is approximately 8 to 11 hours and appears to be independent of dose
3. Iomeprol is almost completely excreted unchanged in urine within 48 hours of injection
4. Renal clearance of Iomeprol is similar to the GFR
IOMERON: Systemic Toxicity

i.v. $LD_{50}$ (g iodine/kg) in mice

- Iopamiro 370
- Iomeron 400
- Optiray 300
- Iohexol 350
- Omnipaque 370
- Iopeaque 350
- Hexabrix 320

* statistically significant difference vs Iomeron

La Noce et al. EJR 1994
Morisetti et al. EJR 1994
Blood Brain Barrier

- Human brain is the most highly perfused organ in the body, being composed of:
  - over 100 billion capillaries
  - with an inter-capillary distance of 50micron
  - a length greater than 600 km

- This network of blood vessels:
  - facilitates the delivery of nutrients and oxygen to the brain
  - while providing a physical, metabolic and immunologic barrier (BBB) to protect it

- BBB comprises a very tight layer of capillary endothelial cells with:
  - elaborate tight junctions between adjacent cells preventing most soluble materials from crossing
  - while allowing gases such as oxygen and carbon dioxide to diffuse through
Neurotoxicity

Intrathecal LD$_{50}$ (g iodine/kg) in mice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intrathecal LD$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iomeron 350</td>
<td>1.4</td>
</tr>
<tr>
<td>Omnipro 350</td>
<td>0.8*</td>
</tr>
<tr>
<td>Visipaque 320</td>
<td>1.0*</td>
</tr>
<tr>
<td>Iopamiro 370</td>
<td>NS 1.5</td>
</tr>
</tbody>
</table>

* Statistically significant difference vs Iomeprol
NS - not significant difference vs Iomeprol

La Noce et al. EJR 1994
Luzzani et al. Invest Radiol 1996

Iomeron 40% < TOXIC than Visipaque
Structure-function relationships of iodinated contrast media and risk of nephrotoxicity

1. Molecular weight is directly related to the size of the molecule

2. Therefore the lower the molecular weight, the smaller the molecule will be

3. **Glomerular filtration is easier with small molecules**, accordingly **low-osmolar and iso-molar CM are generally recommended**

4. **Iomeron® (iomeprol)** has a **lower molecular weight** than a ionic and non-ionic dimer, thus decreasing the likelihood of significant alteration of glomerular filtration and cytotoxicity.

**LOLV-CM**

- Osmolarity/viscosity

- Water recall from interstitium → tubular dilution of CM →
  - ↓ tubular cell uptake of CM
  - ↓ tubular viscosity
  - Osmotic diuresis & faster excretion

**IOHV-CM**

- Iso-osmolar/↑viscosity

- ↑ Vascular resistance & Vasoconstriction
- ↓ Blood Flow → Medullary Ischemia (RBC sludging)
- ↑ Tubular viscosity
  - Tubular obstruction
  - ↑ Interstitial pressure
  - Medullary Ischemia
- ↑ Tubular cell uptake of CM & damage
Pathophysiiological mechanism underlying CIN

NO- nitric oxide, ROS- reactive oxygen species.

adapted from Seeliger et al.
Clinical evidences
Effects of Iodine concentration on HU

30 gl, 2 mL/s, 3 different concentrations

- HU +33% (300 to 400)
- HU +48% (270 to 400)
- HU +25% (320 to 400)
- HU +17% (350 to 400)
- HU +8% (370 to 400)

+18% (340 to 400)
How to compare contrast agents?

Design of a Crossover-Study

1. Blindness of the study
2. Ethics of modality

Major?

Contrast A

Baseline

Randomization

Interval (3-14 days) between doses

Contrast B

Contrast A

Contrast B
MDCT angiography of Pulmonary Arteries: Influence of Iodine Flow Concentration on Vessel Attenuation & Visualization at equi-iodine doses in 100 consecutive patients

IOPROMIDE 300
120 mL

IOMEPROL 400
90 mL

The result was significantly better depiction of fifth-order and sixth-order pulmonary arteries

increased enhancement of the left main pulmonary artery (long arrow) and more uniform visualization of lateral and anterior subsegmental artery of anterior segmental artery of left upper lobe (short arrows), in the same patient

Schoellnast et Al, AJR 2005
How to compare contrast agents?

Prospective, randomized, parallel double blind study

Patient

Baseline

Randomization

Contrast A

Concentration/flow rate A

Blind reading 1-2-3 readers

Contrast B

Concentration/flow rate B

Or further lines of comparison
Iomeron 400 (80 mL, 5 mL/s) of a 47 years old female

Visipaque 320 (80 mL, 5 mL/s) of a 67 years old male

BMI, 36.2 kg/m²

BMI, 28.4 kg/m²

High contrast allows to use increased window level & width (1000 / 300 HU) which reduce the effect of noise.

* Higher enhancement with lower number of inadequately visualized segments

Becker et al., Invest Radiol 2011
High Iodine Concentration Contrast Material in MDCT
Cademartiri et al, Invest Rad 2006

\[ \Delta \text{Attenuation at origin of arteries} \quad P < 0.05 \]

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Δ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average (HU)</td>
<td>312 ± 47</td>
<td>353 ± 59</td>
<td>+41</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Time 0 (HU)</td>
<td>309 ± 45</td>
<td>348 ± 55</td>
<td>+39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MEV (HU)</td>
<td>339 ± 48</td>
<td>390 ± 70</td>
<td>+51</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Measurements of vascular attenuation for the main vessels of the thorax are displayed for group 1 (Ultravist 370) and group 2 (Iomeron 400). Δ, relative difference (group 2 average HU − group 1 average HU).
MDCT angiography for detection of pulmonary emboli

Langenberger et al.  
E J Radiology 2008 e

Study characteristics

- 80 randomized pts received 48 g iodine at 4 mL/s
  - Iomeprol 400 (IOM), 120mL
  - Iodixanol 320 (IOD), 150mL
- scanned by
  - 4-MDCT in 35 pts
  - 64-MDCT in 45 pts
- Lumen attenuation evaluate
  - On site
  - Off site by 2 blinded readers

with improved detection of small PE in distal vessels

Off-site Reading Attenuation values - HU

<table>
<thead>
<tr>
<th></th>
<th>Reader 1 Iomeprol 400</th>
<th>Reader 1 Iodixanol 320</th>
<th>Reader 2 Iomeprol 400</th>
<th>Reader 2 Iodixanol 320</th>
</tr>
</thead>
<tbody>
<tr>
<td>main PA</td>
<td>59</td>
<td>49</td>
<td>80</td>
<td>68</td>
</tr>
<tr>
<td>lobar artery</td>
<td>99</td>
<td>75</td>
<td>99</td>
<td>80</td>
</tr>
<tr>
<td>segmental artery</td>
<td>59</td>
<td>49</td>
<td>80</td>
<td>68</td>
</tr>
<tr>
<td>sub-segmental artery</td>
<td>99</td>
<td>75</td>
<td>99</td>
<td>80</td>
</tr>
</tbody>
</table>

* P < 0.03 at all sites

59 49 80 68 99 75 99 80
Regression lines for each category of region of interest. There is an **increase in opacification**
- 25% for gray matter (A),
- 21% for white matter (B),
- 30% for the arterial input (C),
- 12% for the venous output (D),

between 300- and 400-mg/mL formulations of contrast

---

**Increasing Contrast Agent Concentration Improves Enhancement in First Pass CT Perfusion**

Silvennoine, AJNR 2007

- 102 patients with Acute stroke syndrome
- Iodine g 15
  - Iomeprol 400, 38 mL
  - Iohexol 350, 43 mL
  - Iohexol 300, 50 mL
Abdominal 16 CT - ACTIVE study
Contrast density and heart rate at equi-iodine dose

40 g iodine @ 4 mL/s

Contrast density by off-site blinded Reader 1

Abdominal Aorta
Main Portal Vein
Inferior Vena Cava
Liver parenchyma

Contrast density by off-site blinded Reader 2

Abdominal Aorta
Main Portal Vein
Inferior Vena Cava
Liver parenchyma

Volume mL
Time inj sec
IDR g l / s

IOMEPROL 400
100
25
1,6

IODIXANOL 320
125
31,2
1,28

P < 0.0004
P < 0.04
P = 0.05
P < 0.01

Romano, Br J Rad, 2009
Iomeron & IDR in Dual-Energy CTPA Perfusion Map Images in 100 patients with suspected PE

Protocol B: the best Image Quality

- **IOM 400 - IDR 1.6 gI/s**
  - 80 mL @ 4 mL/s

- **IOM 400 - IDR 1.2 gI/s**
  - 80 mL @ 3 mL/s

- **IOM 300 - IDR 1.6 gI/s**
  - 107 mL @ 5.4 mL/s

- **IOM 300 - IDR 1.2 gI/s**
  - 107 mL @ 4 mL/s

Beam-hardening artifacts

Concentration & IDR Effect on Image Quality

Total Iodine Load = 32 g

Nance et al, Inv Rad 2011
Contrast Induced Nephropathy - CIN

- Risk factors
- Cofactors, including drugs
- Individual susceptibility
- Wide spectrum of clinical manifestations
- Various markers
- Prevention and Therapy
The ACTIVE Trial: Comparison of the Effects on Renal Function of Iomeron 400 and Visipaque 320 in Pts with Chronic Kidney Disease undergoing Abdominal CT

The incidence of CIN was absent / significantly lower after IV administration of Iomeron 400 than Visipaque 320

Thomsen HS et al. Invest Radiol 2008; 43:170-178
Although the “As Low As Reasonably Achievable” (ALARA) principle must be followed in radiation exposure, it must also be remembered that the “As Low As Diagnostically Achievable” (ALADA) standard is required.

Radiation Dose

low-dose protocols: looking for a fair decision!
Low kV Exams

**Iodine enhancement:**

- X-ray absorption higher, since closer to the k-edge*

---

**Graph:**

- At identical iodine concentration

---

1. Low Iodine concentration
2. High Iodine concentration

Waaijer et al. Radiology 2007; 242(3):832
How to compare contrast agents?

Prospective, randomized, parallel double blind study

- Contrast A
  - CT scanner setting A
  - Blind reading 1-2-3 readers

- Contrast B
  - CT scanner setting B

Randomization

Baseline

Patient

Or further lines of comparison
**IOM 400 in low radiation dose protocol**


---

**MDCTA (axial)**

IOM-400 CE images obtained with protocol:

- **A, B-SD** = standard x-ray dose
  - 120-kVp noise index 26
- **C, D-LD** = low x-ray dose
  - 80-kVp noise index 26
- **E, F-ULD** = ultra-low x-ray dose
  - 80-kVp noise index 30

No significant difference between the 3 protocols in mean image quality score (p>0.05)

80 mL of IOM 400, @4mL/s

---

**Figure 1**

- **A**: Aorto iliac
- **B**: Femoro popliteal
- **C**: Standard Dose
- **D**: Low Dose
- **E**: Ultra-Low Dose
Radiation Dose Reduction in DSTA of the entire chest (triple rule-out)

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>kV</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>mAs</td>
<td>320</td>
<td>320</td>
</tr>
<tr>
<td>CM</td>
<td>120 ml</td>
<td>400 mgI/ml</td>
</tr>
<tr>
<td>mgI/ml</td>
<td>@ 4 ml/s</td>
<td>@ 4 ml/s</td>
</tr>
</tbody>
</table>

Standard  Low dose

Radiation Dose Reduction in aortic and iliac MDCTA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I N=43</th>
<th>II N=56</th>
</tr>
</thead>
<tbody>
<tr>
<td>kV</td>
<td>Care Kv 100-120-140</td>
<td></td>
</tr>
<tr>
<td>mAs</td>
<td>330</td>
<td>250</td>
</tr>
<tr>
<td>CM mgl/ml</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>90 ml @ 4 ml/s</td>
<td></td>
</tr>
<tr>
<td>Effective dose (mSv)</td>
<td>8.8</td>
<td>6.1</td>
</tr>
</tbody>
</table>

**TABLE 2: Scan Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Iomeron 300</th>
<th>Iomeron 400</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan range (cm), mean ± SD</td>
<td>69.9 ± 11.3</td>
<td>68.6 ± 11.3</td>
<td>0.36</td>
</tr>
<tr>
<td>Injection flow rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.8 mL/s</td>
<td>8 (19)</td>
<td>5 (9)</td>
<td>0.26</td>
</tr>
<tr>
<td>3.9 mL/s</td>
<td>34 (79)</td>
<td>47 (84)</td>
<td>0.73</td>
</tr>
<tr>
<td>4.0 mL/s</td>
<td>1 (2)</td>
<td>4 (7)</td>
<td>0.54</td>
</tr>
<tr>
<td>Tube potential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 kV</td>
<td>4 (9)</td>
<td>25 (45)</td>
<td>0.0003</td>
</tr>
<tr>
<td>120 kV</td>
<td>24 (56)</td>
<td>28 (50)</td>
<td>0.71</td>
</tr>
<tr>
<td>140 kV</td>
<td>15 (35)</td>
<td>3 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CTDI_v (mGy), mean ± SD</td>
<td>10.9 ± 2.9</td>
<td>4.8 ± 0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLP (mGy-cm), mean ± SD</td>
<td>519 ± 24</td>
<td>360 ± 22</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Schwarz et al. AJR 2013;200:w628-w634
<table>
<thead>
<tr>
<th></th>
<th>I - N=15</th>
<th>II - N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>kV</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>mAs</td>
<td>229</td>
<td>229</td>
</tr>
<tr>
<td>CM mg/l/ml</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>mSv</td>
<td>3.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

MIP

VR

Fine tuning of individual radiation dose reduction protocol

Value of Tailored protocol tool
Tailored Protocols

To compare the diagnostic quality of MDCT exams between patients undergoing MDCT of the chest, abdomen, liver, or aorta with a standard protocol and those scanned with a patient-adapted protocol.

IOMERON
981 patients enrolled

Patients with Standard protocol - St = 497

Patients with Tailored protocol - Tail = 484

968 evaluable
St=491   Tail=477
Clinical validation study: methods

• Clinical centers involved:
  – 7 centers in EU and USA

• Number of adults patients enrolled: 1493
  – Undergoing MDCT examination of the abdomen, liver, chest or aorta
  – Randomized for
    – «standard/conventional»
    – Patient tailored protocol

• Using either Iomeron 400 mg/l of Iopamidol 370 mg/l

• And different scanners
  • GE Lightspeed 16, GE Lightspeed 64, Philips – 40, Philips – 64, Siemens – Sensation 64
Clinical validation study – main results

1. Similar high diagnostic quality of both “conventional” and “tailored protocols”

2. Significant reduction of administered contrast volume, and radiation dose in patients undergoing CT scans with the tailored
Incompatibility of Contrast Medium and Trisodium Citrate *

* a catheter lock solution used as a replacement for heparin in central venous catheters

<table>
<thead>
<tr>
<th>CM (mg/mL)</th>
<th>Brief -Transient precipitation</th>
<th>Permanent precipitation</th>
<th>Gluelike transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omnipaque 240</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Xenetix 350</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Iomeron 400</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Iopromide 370</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Dimer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hexabrix 320</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Visipaque 270</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Visipaque 320</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Iodixanol and ioxaglate provoked a highly viscous gluelike precipitation when mixed with trisodium citrate.

Delcour et al, Cardiovasc Intervent Radiol 2013
Conclusive remarks

The development process proved that the product candidate-**Iomeprol** met the expectations:

- Iomeprol is an *effective and safe contrast medium*
- It is the *most used CM in Europe (> 7 million patients/year)*, both in **CathLab and in Radiology**
- This leadership is lasting from several years
- About 100 million patients were undertaken Iomeprol injection as today
- Reportin Rates of Adverse Events : total < 0.03%
  
  \( \frac{3}{4} \text{ are non-serious and } \frac{1}{4} \text{ are serious} \)
THE BRACCO GROUP

90 YEARS IN THE NAME OF INNOVATION