characteristics of contrast media

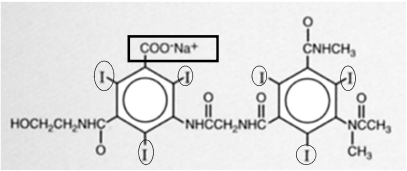
- **Ability to alter the parameters responsible for contrast**
- **The media should possess some tissue specificity**
- **Should be cleared from the organ or tissue in a reasonable period of time**
- **Must have low toxicity and be stable invivo**
- **Suitable shelf life for storage**

Val Runge, MD, 1997

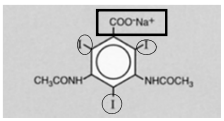
types of iodinated contrast

- **Intravascular**
- **Gastrointestinal**
- **Uroradiological**
- **Intrathecal**

LOCM
(low osmolar contrast media)

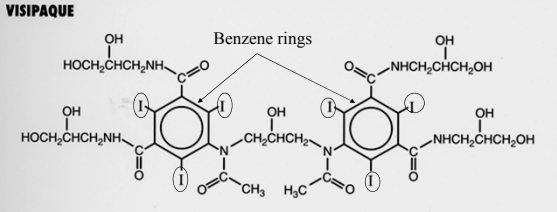


Low osmolar Ionic. For each molecule that dissociates there are 6 atoms of Iodine



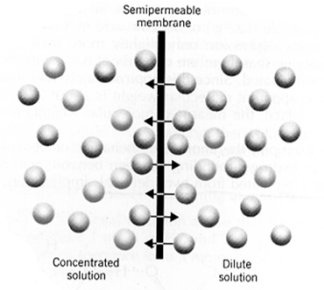
High osmolar ionic. For each molecule that dissociates there are only 3 Iodine atoms

iodinated contrast

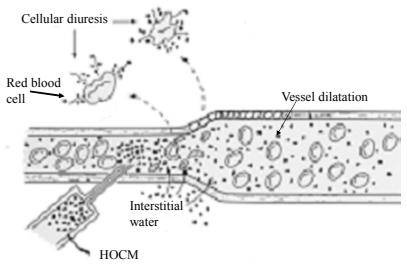


Isosmolar contrast media (IOCM)
nonionic

omosis

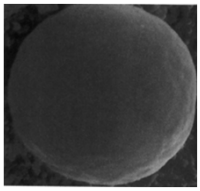


The effect of high osmolar contrast



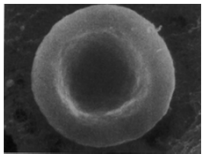
Physiological effects
- **Hypervolemia**
- **Vessel dilatation**
- **Altered erythrocyte morphology**
- **Altered vascular endothelial permeability**

Effect of solutions of varying tonicities on living red blood cells

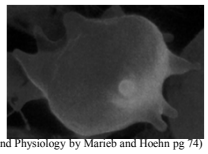


A

B



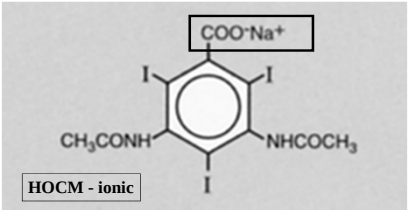
C



A. RBC in hypotonic solution
B. Normal RBC
C. RBC in hypertonic solution, ie., contrast media

(from Human Anatomy and Physiology by Marieb and Hoehn pg 74)

Ionic contrast



HOCM - ionic

Contrast media can cause heart rhythm disturbances. One mechanism is thought to be due to effects on the conducting system that generates the pumping action of the heart

Nonionic CM does not carry electrical charges

osmolality

Osmolality of blood = 285 – 295 mOsm/Kg H_2O

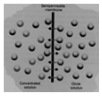
isosmolar CM (visipaque) = 290 mOsm/Kg H_2O

LOCM (optiray 300) = 651 mOsm/Kg H_2O

HOCM (conray 400) = 2300 mOsm/Kg H_2O

MAGNEVIST = 1960 mOsm/Kg H_2O

Osmolality



Osmolality = moles/Kg of solvent

One mole = $\underbrace{6 \times 10^{23}}_{\text{Avogadro's number}}$ particles

MRI contrast material
(extracellular space)

Recommended dose =
0.1 m mole/kg of body weight

(In some cases there is FDA approval for double and triple dose)

.1 m mol in .2 ml

MRI contrast material
(exact dose from package insert)

Recommended dose =
0.1 m mole/kg of body weight
0.1 m mole = .2 ml

$$\frac{\text{200 lb}}{\text{2.2 lb/Kg}} = \text{90.9 Kg}$$

90.9 Kg x 0.2 ml/Kg = 18.18 ml

DOSE CHART

Body Weight		Adult Dosage
Pounds	Kilograms	0.1 mmol/kg Volume (mL)
88	40	8.0
99	45	9.0
110	50	10.0
121	55	11.0
132	60	12.0
143	65	13.0
154	70	14.0
165	75	15.0
176	80	16.0
187	85	17.0
198	90	18.0
209	95	19.0
220	100	20.0
231	105	21.0
242	110	22.0
253	115	23.0
264	120	24.0
275	125	25.0
286	130	26.0
297	135	27.0
308	140	28.0
319	145	29.0
330	150	30.0

From:
www.multihanceusa.com

osmotic load

Magnevist – an ionic gadolinium contrast

- **Osmolality = 1960 mOsm/Kg**
- **Total osmotic load = 27 mOsm (14 ml / 70 kg)**

Omnipaque 300 – a nonionic Iodinated contrast

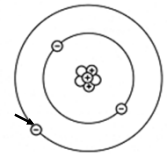
- **Osmolality = 672 mOsm/kg**
- **Total osmotic load = 101 mOsm (150 ml injection)**

osmotic load

Contrast	Osmolality Mmol/kg	Relaxivity (enhancement)
Magnevist	1960	4
Prohance (Memorial)	630	3.7
Multihance (Memorial)	1970	9

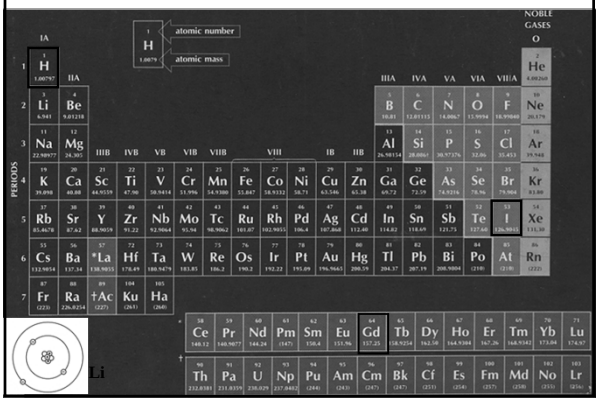
paramagnetic contrast

- **Shortens T1 time of tissues**
- **Atoms are magnetic because of their outer layer of electrons**



Lithium with atomic shells one unpaired electron

PERIODIC TABLE OF ELEMENTS



types of mri contrast

- **Extracellular agents**
- **Hepatobilliary agents**
- **Oral agents**
- **Blood–pool agents**

types of mri contrast (experimental)

- Liver spleen agents
- Lymph node agents
- Tumor specific agents

extracellular paramagnetic agents

- Extracellular space is the sum of intravascular space and interstitial space
- Paramagnetic agents diffuse across the capillaries into the interstitial space of tissues (outside of the cns) and across the renal glomeruli into the urinary collecting system

arterial phase

- First 30 seconds after injection
- Useful for depicting tissue perfusion
- Useful for depicting tissue vascularity
- Enhancement of pancreas, renal cortex and spleen
- Absence of renal parenchyma enhancement
- Minimal enhancement of liver parenchyma

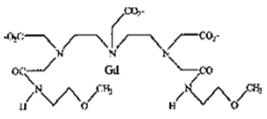
blood pool phase
(or portal vein phase)

- **Less than a minute post injection**
- **Contrast distributed throughout the body's blood vessels**
- **Phase of maximum hepatic enhancement**

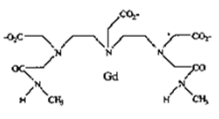
extracellular phase

- **images acquired at least 2 min after injection**
- **Contrast diffuses across capillaries into interstitium (Capillaries of the brain and testes are not permeable to contrast)**
- **Enhancement of edematous tissues (neoplasms) and inflammation**
- **Mets which have large interstitial spaces enhance**

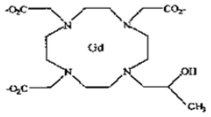
MRI IV contrasts



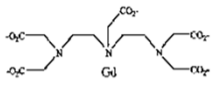
Optimark – nonionic, linear



Omniscan – nonionic, linear

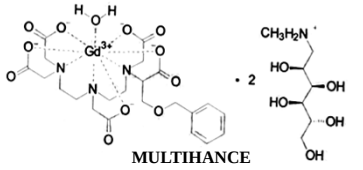


ProHance – nonionic, cyclical



Magnevist – ionic, linear

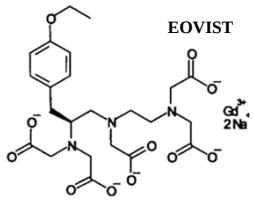
MRI IV contrasts



MULTIHANCE

- **Linear, ionic**
- **Has twice the relaxivity of other gadolinium contrasts so it enhances more**
- **Has the ability to weakly and transiently bind with blood serum albumin**
- **4% of the multihance injected is eliminated thru the liver**
- **Safety profile is similar to the other gadolinium extracellular space agents**

MRI IV contrasts



EOVIST

- Liver-specific agent
- Allows greater contrast enhancement between healthy liver parenchyma and malignant tissue during the hepatocyte phase
- Higher relaxivity ≈8.7 (Multihance ≈9, Magnevist ≈4)
- 50% eliminated thru the kidneys and 50% thru the heptobiliary system
- Dose = 1/2 of the approved (ml) dose of other agents

Dose

Eovist 0.025 mmole/kg = 0.1 ml/kg

200 lb = 90.8 kg

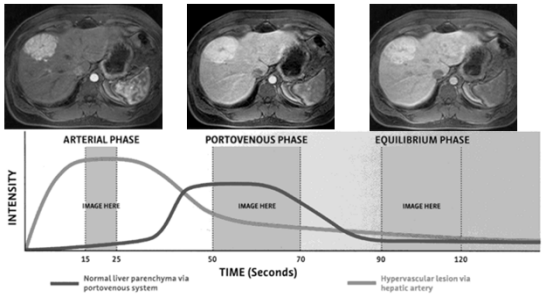
90.8 kg x .1 ml/kg = 9.08 ml

Multihance 0.1 mmole/Kg = 0.2 ml/Kg

90.8 kg x .2 ml/kg = 18.1 ml

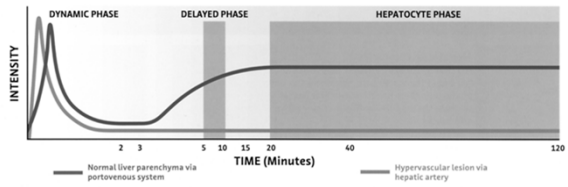
Eovist

(from Bayer HealthCare Pharmaceuticals Inc.)



Eovist

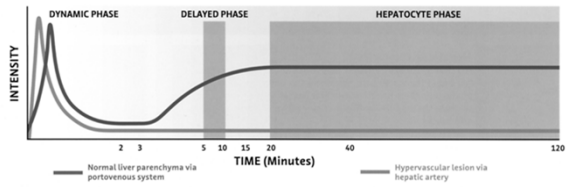
(from Bayer HealthCare Pharmaceuticals Inc.)



1. **Lesions like metastases, cholangiocarcinomas do not have hepatocytes are dark**
2. **During the hepatocyte phase normal parenchyma accumulates Eovist and it is bright**

Eovist

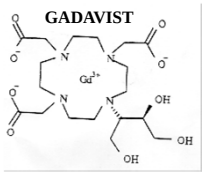
(from Bayer HealthCare Pharmaceuticals Inc.)



3. **Poorly differenciated hepatocellular ca (HCC) are dark and well differenciated HCC hyperintense to normal parenchyma**
4. **Focal nodular hyperplasias (FNH), adnedomas and hemangiomas are hypointense to liver**

MRI IV contrasts

GADAVIST



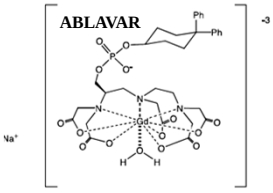
- Dose = .1 ml/Kg
- Relaxivity ≈ 5
  (Magnevist ≈4,
  higher relaxivity Multihance ≈9,
  Eovist ≈8.7)
- ≈100% eliminated thru the kidneys, extra renal excretion negligible

130 lb ./. 2.2lb/Kg = 59.1 Kg

59.1Kg x .1 ml/Kg = 5.91 ml

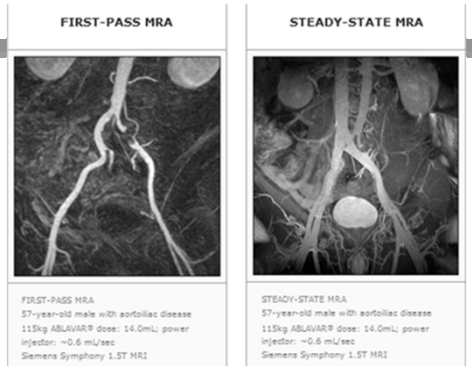
MRI IV contrasts

ABLAVAR



- Less Gadolinium used
- Binds to serum albumin, like Multihance
- Extended intravascular retention
- Increased relaxivity ≈ or > 19
  - Magnevist ≈4
  - Multihance ≈9
  - Eovist ≈8.7
- 94% eliminated in urine within 72 hrs and 4.7% in feces

ablavar



Note: regular dose about 6 ml

MRI IV contrasts

	Gd dose Mmole/Kg	Volume ml/Kg	Gd dose in mmole/Kg for 70 Kg patient	Gd dose in ml for 70 Kg patient
Ablavar	**0.03**	**0.12**	**2.1**	**8.4 ml**
***regular* GBCM**	**0.1**	**0.2**	**14**	**14 ml**

Adverse effects of gadolinium contrast

TABLE 2. Adverse reaction incidence data from product package inserts (%)

Agent	Magnevist	ProHance	Omniscan	OptiMARK
Headache	4.8	<1.0	≤ 3.0	9.4
Nausea	2.7	1.4	≤ 3.0	3.2
Dizziness	1.0	<1.0	≤ 3.0	3.7
Vasodilatation	<1.0	<1.0	≤ 1.0	6.4
Taste perversion	<1.0	1.4	≤ 1.0	6.2

Sources: Package Inserts: (Magnevist 2000, ProHance 1999, Omniscan 1997, OptiMARK 2000)

contrast reactions

(from ACR Manual on Contrast Media Version 7, 2010)

- **mild**
- **moderate**
- **severe**
- **organ specific**

organ specific reactions

(from ACR Manual on Contrast Media Version 7, 2010)

- Adrenal - hypotension
- CNS – headache, confusion, dizziness, diminished or loss of consciousness or loss of vision
- Heart - hypotension, dysrythmias, pulseless electrical activity, acute congestive heart failure
- Kidney - oliguria, hypertension

organ specific reactions

(from ACR Manual on Contrast Media Version 7, 2010)

- GI tract - nausea, vomiting, diarrhea, cramping
- Pancreas - swelling
- Respiratory system - bronchospasm, laryngeal / pulmonary edema
- Salivary glands - swelling
- Skin - pain, swelling, heat, erythema, urticaria, pruritus
- Thyroid - worsening of thyrotoxicosis

mild contrast reactions

(from ACR Manual on Contrast Media Version 7, 2010)

- do not require treatment
- require monitoring for at least 20 - 30 min
- nausea vomiting urticaria pain on injection

moderate contrast reactions

(from ACR Manual on Contrast Media Version 7, 2010)

Require treatment and close monitoring

- **Urticaria - diphenhydramine**
- **vasovagal reactions, hypotension - leg elevation**
- **Bronchospasms – beta-agonist inhaler**
- **Tachycardia**
- **Laryngeal edema - epinephrine**

severe contrast reactions

(from ACR Manual on Contrast Media Version 7, 2010)

- **Potentially or immediately life threatening**
- **Low rate but unpredictable**
- **Range from anxiety to sudden cardiac arrest**
- **Vasovagal reactions, bronchospasms, (anaphylaxis) anaphylactoid reaction**

don't *panic!*

Stop. Think. Act.

Get the appropriate help immediatelly

¡CPR!

Start CPR if ABC's are compromised

epinephrine

- **E** **Every**
- **P** **Pulseless**
- **I** **Individual**

gadolinium reactions
ACR Manual on Contrast Media
version 7.0, 2010

- **Frequency of adverse events (non allergic, mild, moderate, severe) range from 0.07%-2.4%**
- **Rxns resembling an "allergic" response range from 0.004% - 0.7%**

gadolinium reactions
ACR Manual on Contrast Media version 7.0 2010

- "severe, life-threatening anaphylactoid reactions are exceedingly rare (0.001%-0.01%)"
- "in an accumulated series of 687,000 doses there were only 5 severe reactions"
- In another survey based on 20 million administered doses there were 55 cases of anaphylactoid shock"

iodine reactions
ACR Manual on Contrast Media version 7.0, 2010

- In the old days (with use of HOCM) reactions were as high as 5%-15%
- With LOCM rates are reportedly down to .2% - .6%
- Delayed reactions reportedly up to 2%: nausea, headache, pruritus, iodide mumps (salivary gland swelling), CIN

CIN and Iodine
(ACR Manual on Contrast Media version 7.0, 2010)

- Risk factors:
  - Pre-existing renal disease
  - Diabetes mellitus
  - Dehydration
  - Cardiovascular disease
  - Advanced age
  - Multiple myeloma
  - Hypertension
  - Hyperuricemia (↑ uric acid)

Preliminary considerations before injecting contrast media

- Assessment of patient risk versus potential benefits
- Imaging alternatives
- Assurance of a valid clinical indication

Preliminary considerations before injecting contrast media the 4 H's

- History
- Hydration
- Have equipment and expertise available
- Heads up be aware of risks

Patient selection and preparation

- Prior allergic reaction to contrast media
- Patient with significant allergic reactions with a prior anaphylactic response to an allergen
- Allergies to seafood or shellfish are considered unreliable
- Significant cardiac disease has an increased risk
- Reducing anxiety may reduce incidence of rxn

Premedication against allergies

- Pretesting is not recommended and may in itself be dangerous
- Pretreatment does not eliminate the risk of a reaction
- 32 mg Medrol 12 hrs before and 2 hrs before

or

- 50 mg prednisone 13 hrs, 7 hrs and 1 hrs before
- Benadryl 50mg IV or IM or PO 1 hr before
- Non ionic LOCM

NFD/NSF

Nephrogenic Fibrosing Dermopathy

Nephrogenic Systemic Fibrosis

What is NSF?

(from the FDA
Center for Drug Evaluation and Research and Public Health Advisory, Dec 22, 2006 and the National Kidney Foundation)

- Uncommon condition – first reported in 1997. Hundreds of cases have been reported to the NFD Registry
- Unknown cause
- Idiopathic disorder that manifests on patients with renal disease
- No infectious agent has been identified

What is NSF?

(from the FDA
Center for Drug Evaluation and Research and Public Health Advisory, Dec 22, 2006 and the National Kidney Foundation)

- Fibrotic process affects subcutaneous tissue, fascia, striated muscles, myocardium in addition to the dermis
- Within weeks of the disease onset, many patients become dependent on wheelchair because of contractures
- Patient die because of complications from fractures after falls

What is NSF?

(from the FDA
Center for Drug Evaluation and Research and Public Health Advisory, Dec 22, 2006 and the National Kidney Foundation)

- Patients complain about maddening pruritus and or causalgia (intense burning pain)
- Flexion contractures
- Skin can have a peau d'orange appearance and shiny look and feel hard to the touch

FDA Public Health Advisory on NSF, Dec 22, 2006

"Update on Magnetic Resonance Imaging (MRI) Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermopathy"

Notification:

"Patients with moderate to end stage kidney disease who receive and MRI or MRA with a gadolinium-based contrast agent may get NFS/NFD which is debilitating and may cause death"

Nephrogenic Fibrosing Dermopathy
(Public Health Advisory, Dec 22, 2006)

- FDA received reports of 90 cases with moderate to end stage renal disease who developed NFD after receiving Gadolinium contrast for MRI/MRA
- Patients developed NFD 2 days – 18 months after exposure to the contrast

Nephrogenic Systemic Fibrosis
(ACR Guidance Document for Safe MR Practices: 2007)

- As of Jan 2007 FDA's Med Watch had more that 100 cases of NSF
  - 85 Omniscan
  - 21 Magnevist
  - 6 Optimark
  - 1 Multihance + Omniscan
  - 0 Prohance
- As 2010 the NSF reports 335 cases

Nephrogenic Systemic Fibrosis
(ACR Guidance Document for Safe MR Practices: 2007)

"The incidence of developing NFS by patients with severe or end stage renal disease after being administered Omniscan appears to be roughly only 3-5%" **

** Investigation of the safety of MRI contrast medium, Omniscan, May 29,2006,(last updated January, 2007) Danish Medicines Agency Website: www.dkma.dk

FDA alert update
May 23,2007

"Requests for addition of a boxed warning and new warnings about risk of NSF to the full prescribing information for all gadolinium based contrast agents…"

FDA alert update
May 23,2007
(request for boxed warning in medication insert)

requests … "new labeling highlights and describes the risk for NFS following exposure to GBCA in patients with acute or chronic severe renal insufficiency (a glomerular filtration rate <30mL/min/1.73m^2)

GFR >30 for contrast

Glomerular Filtration Rate (GFR)
NKF

stages of renal disease

- **stage 1 & 2**
  - **presence of kidney damage but GFR > 90mL/min/1.73m^2**
  - **no action needs to be taken**
- **stage 3**
  - **moderate chronic kidney disease**
  - **GFR between 30 – 59 mL/min/1.73m^2**

Glomerular Filtration Rate (GFR) NKF

stages of renal disease

- **stage 4**
  - **GFR between 15 – 29 mL/min/1.73m²**
  - **severe CKD**
- **stage 5**
  - **in dialysis or end stage CDK**
  - **moderate chronic kidney disease**
  - **GFR < 15 mL/min/1.73m²**

However…,

stage 3

the ACR recommends:

eGFR 45-59 → lowest possible dose
eGFR 30-44 → avoid use of GBCM,
lowest possible dose,
avoid use "Group 1" Gad agents

Group I

Agents associated with the greatest number of NSF cases

AGENT	# OF DOSES (IN MILLIONS)	# OF NFS CASES
Omniscan	13	382
Magnevist	23	195
Optimark	4.7	35

Group II

Agents associated with few, if any, cases of NSF

- **Multihance**
- **Prohance**
- **Gadovist**
- **Dotarem – not FDA approved**

Group III

New agents with limited data, although few if any cases of NSF

- **Eovist**
- **Ablavar**

FDA alert update recommendations May 23,2007

Become familiar with the populations at risk

Avoid using GBCA in patients with known risks unless the diagnostic information is essential and cannot be obtained with non-contrast enhanced MRI or other diagnostic procedures

Evaluate for renal function by obtaining a medical history and/or conducting lab tests

FDA alert update recommendations May 23,2007

- When administering GBCA do not exceed the recommended dose in product labeling
- Allow a sufficient period of time for elimination of the agent from the body.
- For patients receiving hemodialysis, consider prompt hemodialysis after administration of a GBCA.

FDA alert update recommendations May 23,2007

- Published data indicate that hemodialysis enhances GBCA elimination.
- From the first to the third session, reported average GBCA clearance rates were 78%, 96% and 99%, respectively.

safety

"...in general, all four of the gadolinium based contrast agents are among the safest drugs that we as diagnostic radiologists use"

Emanuel Kanal, MD
Director of Magnetic Resonance Services, Professor,
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