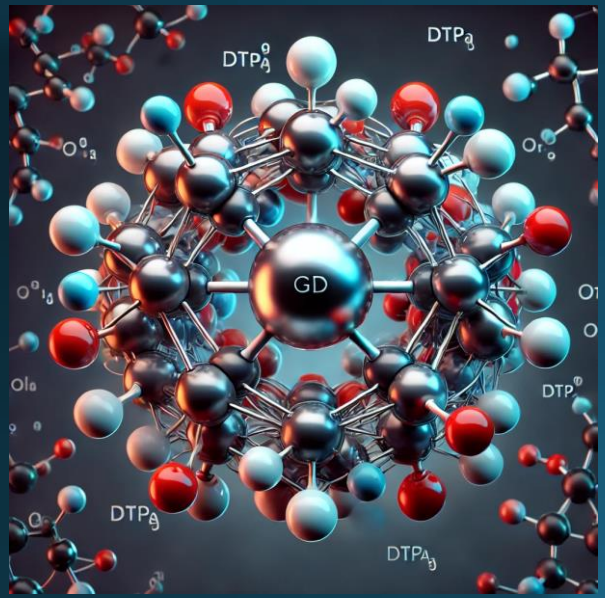
MRI Contrast Agents: When to use contrast, what to use and why?

Olivier Lucidarme

Sorbonne university, Paris France

Objective

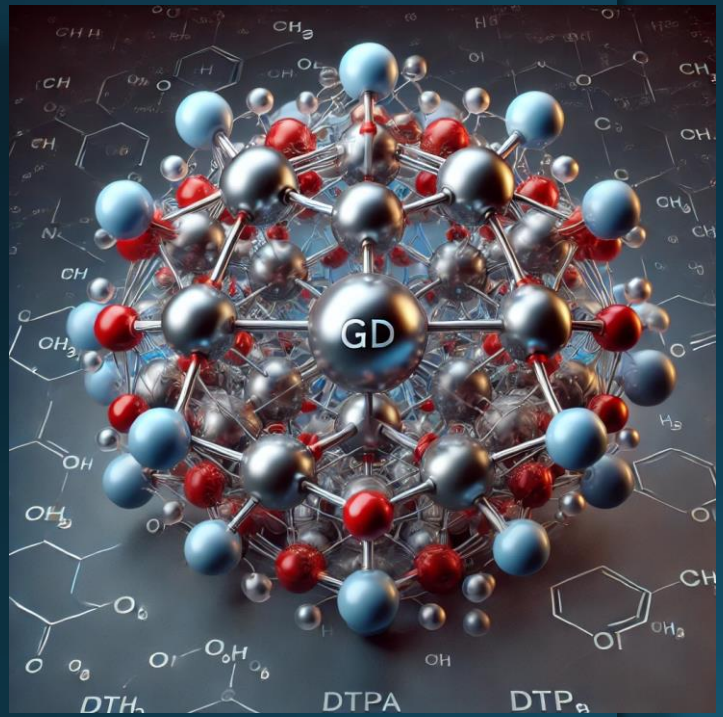


Safety and Optimal **quality of care**

1. Patient safety
2. Environmental safety

1. When or when not ?
2. Which GBCAs

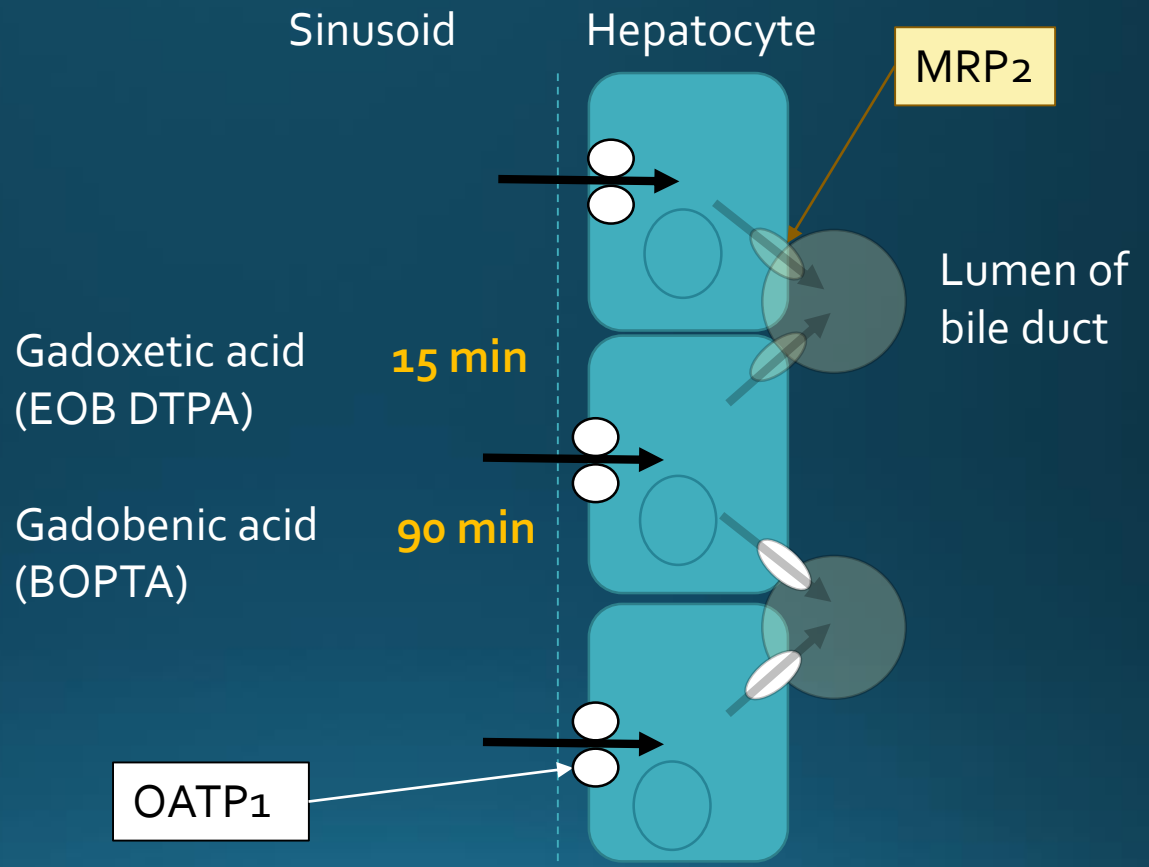
Gd Based contrast agents (GBCAs)



- $Gd^{3+}$is a heavy metal = Toxicity
- To prevent this toxicity Gd ion is chelated ➔ GBCAs as stable as possible
- Free Gd^{3+} accumulates in spleen, liver, bone, brain, kidney, skin etc
  - → NSF *(Renal impairment & Linear GBCAs)*
  - → Brain deposit (all GBCA but Linear >> Macrocyclic)
- The heavy metal can pollute the environment when patients excrete it
  - → Impacting water sources and ecosystems

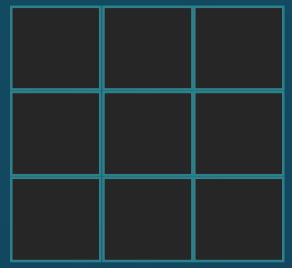
Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear	Gadoxetate disodium	Primovist® (Bayer)	<5s at 25°C	23.5 (18.7)	50% Kidney 50% Bile	1.5 h	6.9 (6.2)	0.025 mmol/kg (=0.1ml/kg)
	Gadobenate dimeglumine	MultiHance® (Bracco)	<5s at 25°C	22.6 (18.4)	97% Kidney 3% Bile	1.5 h	6.3 (5.5)	0.1 mmol/kg (0.2ml/kg)
Cyclic	Gadoterate meglumine	Dotarem® (Guerbet)	4 days at 37°C	25.6 (19.3)	Kidney	1.4-2.0h (F-M)	3.6 (3.5)	0.1 mmol/kg (0.2ml/kg)
	Gadoteridol	ProHance® (Bracco)	4.0 h at 37°C	23.8 (17.1)	Kidney	1.57h	4.1 (3.7)	0.1 mmol/kg (0.2 ml/kg)
	Gadobutrol	Gadovist® (Bayer)	18 h at 37°C	21.8 (14.7)	Kidney	1.8h	5.2 (5)	0.1 mmol/kg (0.1ml/kg)
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)	20 days at 37°C	18.7 (15.5)	Kidney	1.5h	12.2 (11.3)	0.05 mmol/kg (=0.1ml/kg)
	Gadoquatrane	Bayer (Phase III)	21 days at 37°C		Kidney		11.8 (10.5)	0.04 mmol/kg

The two intracellular linear GBCAs?



OATP1 : Organic Anion Transporting Polypeptide 1
MRP2 : Multidrug Resistance Protein 2

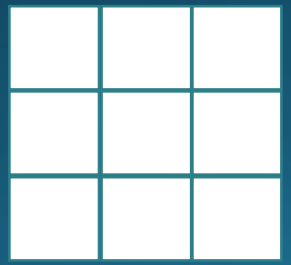
Hepatobiliary phase



Liver

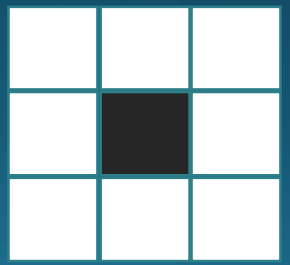
Gadoxetic acid (EOB DTPA) 15′
Gadobenic acid (BOPTA) 90′

Functional hepatocytes OATP1 +



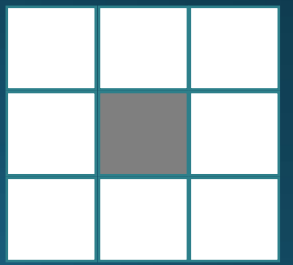
Enhancement

no hepatocyte OATP1 -



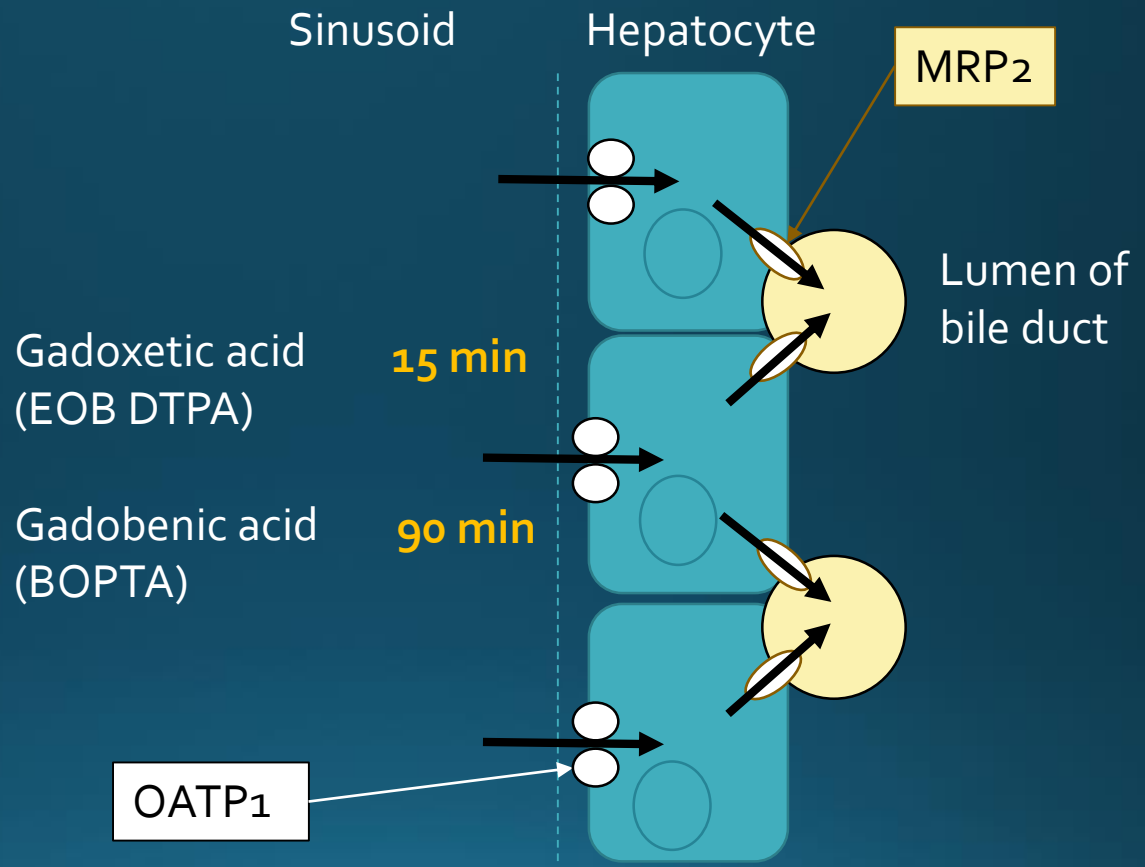
No enhancement

Abnormal hepatocytes OATP1 +/-



No or lower enhancement

The two intracellular linear GBCAs?



OATP1 : Organic Anion Transporting Polypeptide 1
MRP2 : Multidrug Resistance Protein 2

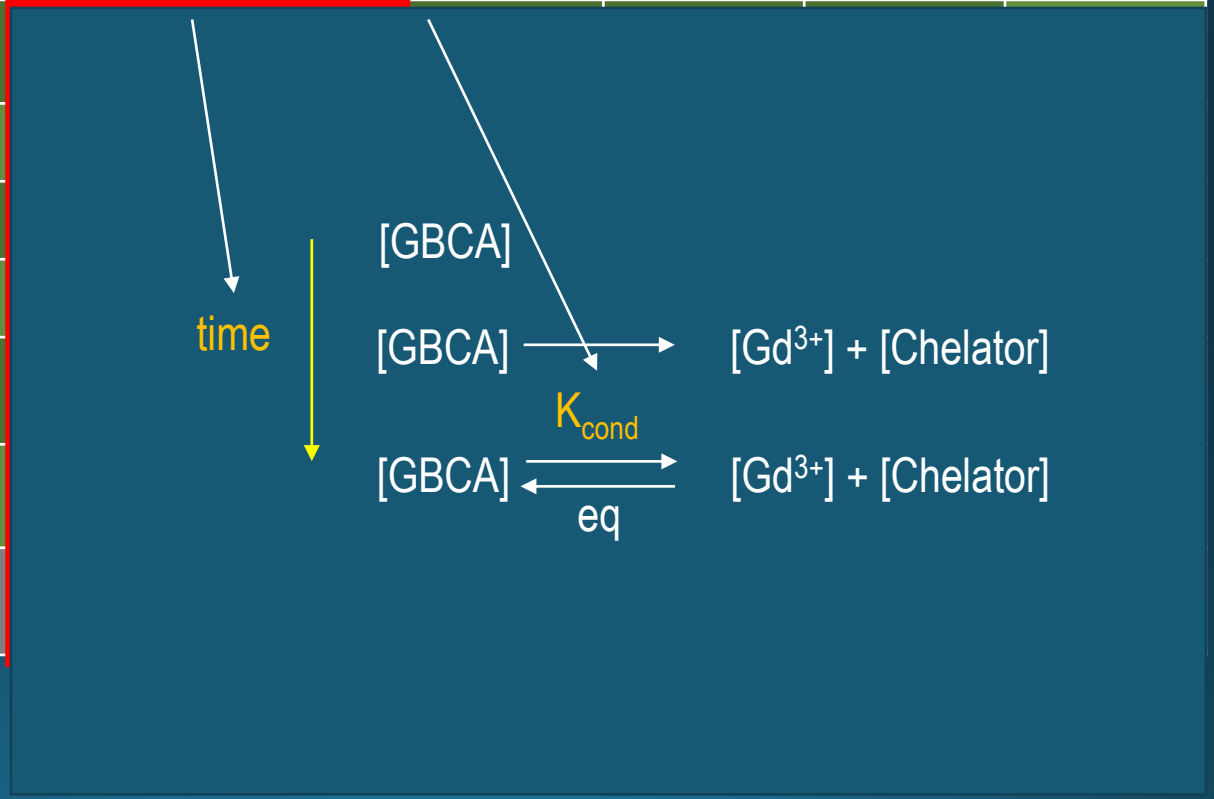
Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear	Gadoxetate disodium	Primovist® (Bayer)	<5s at 25°C	23.5 (18.7)	50% Kidney 50% Bile	1.5 h	6.9 (6.2)	0.025 mmol/kg (=0.1ml/kg)
	Gadobenate dimeglumine	MultiHance® (Bracco)	<5s at 25°C	22.6 (18.4)	97% Kidney 3% Bile	1.5 h	6.3 (5.5)	0.1 mmol/kg (0.2ml/kg)
Cyclic	Gadoterate meglumine	Dotarem® (Guerbet)	4 days at 37°C	25.6 (19.3)	Kidney	1.4-2.0h (F-M)	3.6 (3.5)	0.1 mmol/kg (0.2ml/kg)
	Gadoteridol	ProHance® (Bracco)	4.0 h at 37°C	23.8 (17.1)	Kidney	1.57h	4.1 (3.7)	0.1 mmol/kg (0.2 ml/kg)
	Gadobutrol	Gadovist® (Bayer)	18 h at 37°C	21.8 (14.7)	Kidney	1.8h	5.2 (5)	0.1 mmol/kg (0.1ml/kg)
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)	20 days at 37°C	18.7 (15.5)	Kidney	1.5h	12.2 (11.3)	0.05 mmol/kg (=0.1ml/kg)
	Gadoquatrane	Bayer (Phase III)	21 days at 37°C		Kidney		11.8 (10.5)	0.04 mmol/kg

Only for liver Imaging (without any alternative)

Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear	Gadoxetate disodium	Primovist® (Bayer)	<5s at 25°C	23.5 (18.7)	50% Kidney 50% Bile	1.5 h	6.9 (6.2)	0.025 mmol/kg (=0.1ml/kg)
	Gadobenate dimeglumine	MultiHance® (Bracco)	<5s at 25°C	22.6 (18.4)	97% Kidney 3% Bile	1.5 h	6.3 (5.5)	0.1 mmol/kg (0.2ml/kg)
Cyclic	Gadoterate meglumine	Dotarem® (Guerbet)	4 days at 37°C	25.6 (19.3)	Kidney	1.4-2.0h (F-M)	3.6 (3.5)	0.1 mmol/kg (0.2ml/kg)
	Gadoteridol	ProHance® (Bracco)	4.0 h at 37°C	23.8 (17.1)	Kidney	1.57h	4.1 (3.7)	0.1 mmol/kg (0.2 ml/kg)
	Gadobutrol	Gadovist® (Bayer)	18 h at 37°C	21.8 (14.7)	Kidney	1.8h	5.2 (5)	0.1 mmol/kg (0.1ml/kg)
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)	20 days at 37°C	18.7 (15.5)	Kidney	1.5h	12.2 (11.3)	0.05 mmol/kg (=0.1ml/kg)
	Gadoquatrane	Bayer (Phase III)	21 days at 37°C		Kidney		11.8 (10.5)	0.04 mmol/kg

Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear	Gadoxetate disodium	Primovist® (Bayer)	<5s at 25°C	23.5 (18.7)	50% Kidney 50% Bile	1.5 h	6.9 (6.2)	0.025 mmol/kg (=0.1ml/kg)
	Gadobenate dimeglumine	MultiHance® (Bracco)	<5s at 25°C	22.6 (18.4)	97% Kidney 3% Bile	1.5 h	6.3 (5.5)	0.1 mmol/kg (0.2ml/kg)
Cyclic	Gadoterate meglumine	Dotarem® (Guerbet)	4 days at 37°C	25.6 (19.3)	Kidney	1.4-2.0h (F-M)	3.6 (3.5)	0.1 mmol/kg (0.2ml/kg)
	Gadoteridol	ProHance® (Bracco)	4.0 h at 37°C	23.8 (17.1)	Kidney	1.57h	4.1 (3.7)	0.1 mmol/kg (0.2 ml/kg)
	Gadobutrol	Gadovist® (Bayer)	18 h at 37°C	21.8 (14.7)	Kidney	1.8h	5.2 (5)	0.1 mmol/kg (0.1ml/kg)
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)	20 days at 37°C	18.7 (15.5)	Kidney	1.5h	12.2 (11.3)	0.05 mmol/kg (=0.1ml/kg)
	Gadoquatrane	Bayer (Phase III)	21 days at 37°C		Kidney		11.8 (10.5)	0.04 mmol/kg

Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear	Gadoxetate disodium	Primovist® (Bayer)						
	Gadobenate dimeglumine	MultiHance® (Bracco)						
Cyclic	Gadoterate meglumine	Dotarem® (Guerbet)						
	Gadoteridol	ProHance® (Bracco)						
	Gadobutrol	Gadovist® (Bayer)						
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)						
	Gadoquatrane	Bayer (Phase III)						



Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear	Gadoxetate disodium	Primovist® (Bayer)	<5s at 25°C	23.5 (18.7)	50% Kidney 50% Bile	1.5 h	6.9 (6.2)	0.025 mmol/kg (=0.1ml/kg)
	Gadobenate dimeglumine	MultiHance® (Bracco)	<5s at 25°C	22.6 (18.4)	97% Kidney 3% Bile	1.5 h	6.3 (5.5)	0.1 mmol/kg (0.2ml/kg)
Cyclic	Gadoterate meglumine	Dotarem® (Guerbet)	4 days at 37°C	25.6 (19.3)	Kidney	1.4-2.0h (F-M)	3.6 (3.5)	0.1 mmol/kg (0.2ml/kg)
	Gadoteridol	ProHance® (Bracco)	4.0 h at 37°C	23.8 (17.1)	Kidney	1.57h	4.1 (3.7)	0.1 mmol/kg (0.2 ml/kg)
	Gadobutrol	Gadovist® (Bayer)	18 h at 37°C	21.8 (14.7)	Kidney	1.8h	5.2 (5)	0.1 mmol/kg (0.1ml/kg)
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)	20 days at 37°C	18.7 (15.5)	Kidney	1.5h	12.2 (11.3)	0.05 mmol/kg (=0.1ml/kg)
	Gadoquatrane	Bayer (Phase III)	21 days at 37°C		Kidney		11.8 (10.5)	0.04 mmol/kg

Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear	Gadoxetate disodium	Primovist® (Bayer)	<5s at 25°C	23.5 (18.7)	50% Kidney 50% Bile	1.5 h	6.9 (6.2)	0.025 mmol/kg (=0.1ml/kg)
	Gadobenate dimeglumine	MultiHance® (Bracco)	<5s at 25°C	22.6 (18.4)	97% Kidney 3% Bile	1.5 h	6.3 (5.5)	0.1 mmol/kg (0.2ml/kg)
Cyclic	Gadoterate meglumine	Dotarem® (Guerbet)	4 days at 37°C	25.6 (19.3)	Kidney	1.4-2.0h (F-M)	3.6 (3.5)	0.1 mmol/kg (0.2ml/kg)
	Gadoteridol	ProHance® (Bracco)	4.0 h at 37°C	23.8 (17.1)	Kidney	1.57h	4.1 (3.7)	0.1 mmol/kg (0.2 ml/kg)
	Gadobutrol	Gadovist® (Bayer)	18 h at 37°C	21.8 (14.7)	Kidney	1.8h	5.2 (5)	0.1 mmol/kg (0.1ml/kg)
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)	20 days at 37°C	18.7 (15.5)	Kidney	1.5h	12.2 (11.3)	0.05 mmol/kg (=0.1ml/kg)
	Gadoquatrane	Bayer (Phase III)	21 days at 37°C		Kidney		11.8 (10.5)	0.04 mmol/kg

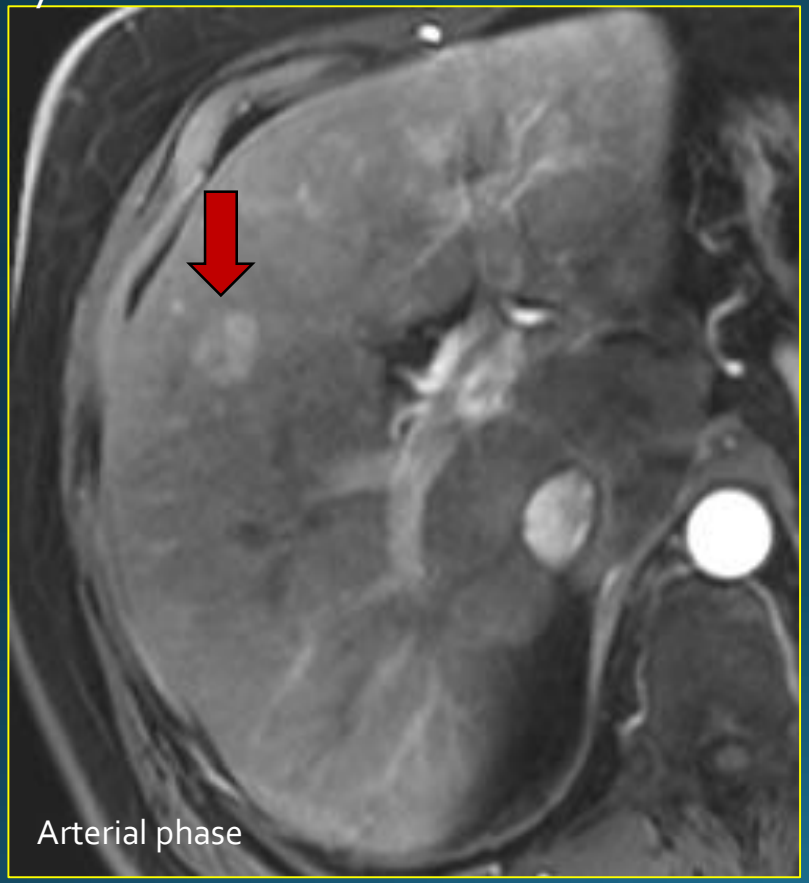
Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear **Liver Only**	Gadoxetate disodium	Primovist® (Bayer)	<5s at 25°C	23.5 (18.7)	50% Kidney 50% Bile	1.5 h	6.9 (6.2)	0.025 mmol/kg (=0.1ml/kg)
	Gadobenate dimeglumine	MultiHance® (Bracco)	<5s at 25°C	22.6 (18.4)	97% Kidney 3% Bile	1.5 h	6.3 (5.5)	0.1 mmol/kg (0.2ml/kg)
Cyclic **General Use**	Gadoterate meglumine	Dotarem® (Guerbet)	4 days at 37°C	25.6 (19.3)	Kidney	1.4-2.0h (F-M)	3.6 (3.5)	0.1 mmol/kg (0.2ml/kg)
	Gadoteridol	ProHance® (Bracco)	4.0 h at 37°C	23.8 (17.1)	Kidney	1.57h	4.1 (3.7)	0.1 mmol/kg (0.2 ml/kg)
	Gadobutrol	Gadovist® (Bayer)	18 h at 37°C	21.8 (14.7)	Kidney	1.8h	5.2 (5)	0.1 mmol/kg (0.1ml/kg)
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)	20 days at 37°C	18.7 (15.5)	Kidney	1.5h	12.2 (11.3)	0.05 mmol/kg (=0.1ml/kg)
	Gadoquatrane	Bayer (Phase III)	21 days at 37°C		Kidney		11.8 (10.5)	0.04 mmol/kg

continue to be used in their indications only, when necessary,
at the lowest possible dose

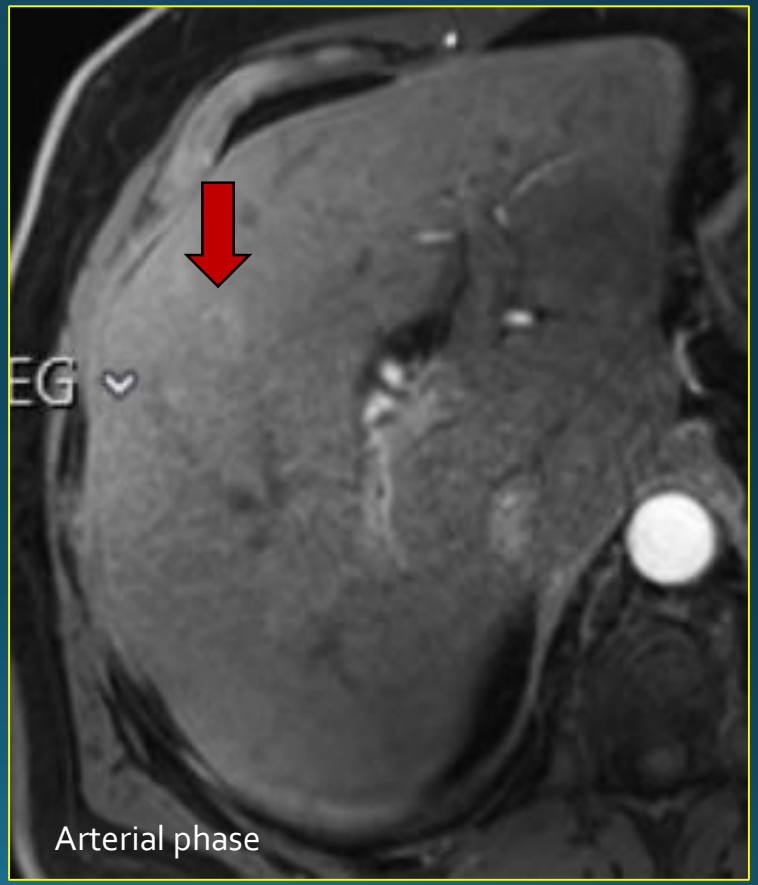
Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear **Liver Only**	Gadoxetate disodium	Primovist® (Bayer)	<5s at 25°C	23.5 (18.7)	50% Kidney 50% Bile	1.5 h	6.9 (6.2)	0.025 mmol/kg (=0.1ml/kg)
	Gadobenate dimeglumine	MultiHance® (Bracco)	<5s at 25°C	22.6 (18.4)	97% Kidney 3% Bile	1.5 h	6.3 (5.5)	0.1 mmol/kg (0.2ml/kg)
Cyclic **General Use**	Gadoterate meglumine	Dotarem® (Guerbet)	4 days at 37°C	25.6 (19.3)	Kidney	1.4-2.0h (F-M)	3.6 (3.5)	0.1 mmol/kg (0.2ml/kg)
	Gadoteridol	ProHance® (Bracco)	4.0 h at 37°C	23.8 (17.1)	Kidney	1.57h	4.1 (3.7)	0.1 mmol/kg (0.2 ml/kg)
	Gadobutrol	Gadovist® (Bayer)	18 h at 37°C	21.8 (14.7)	Kidney	1.8h	5.2 (5)	0.1 mmol/kg (0.1ml/kg)
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)	20 days at 37°C	18.7 (15.5)	Kidney	1.5h	12.2 (11.3)	0.05 mmol/kg (=0.1ml/kg)
	Gadoquatrane	Bayer (Phase III)	21 days at 37°C		Kidney		11.8 (10.5)	0.04 mmol/kg

continue to be used in their indications only, when necessary,
at the lowest possible dose

Courtesy Pr Dow-Mu Koh



Gadopiclinol



Gadoterate Meglumine

Chemical structure	Generic name	Trade Name	Kinetic stability ($T_{1/2}$ at PH 1,0)	Thermodynamic stability Log K_{cond}	Elimination way	Half life	Relaxivity $mM^{-1}.s^{-1}$ 1.5T (3T)	Recommended dose
Linear	Gadoxetate disodium	Primovist® (Bayer)	<5s at 25°C	23.5 (18.7)	50% Kidney 50% Bile	1.5 h	6.9 (6.2)	0.025 mmol/kg (=0.1ml/kg)
	Gadobenate dimeglumine	MultiHance® (Bracco)	<5s at 25°C	22.6 (18.4)	97% Kidney 3% Bile	1.5 h	6.3 (5.5)	0.1 mmol/kg (0.2ml/kg)
Cyclic	Gadoterate meglumine	Dotarem® (Guerbet)	4 days at 37°C	25.6 (19.3)	Kidney	1.4-2.0h (F-M)	3.6 (3.5)	0.1 mmol/kg (0.2ml/kg)
	Gadoteridol	ProHance® (Bracco)	4.0 h at 37°C	23.8 (17.1)	Kidney	1.57h	4.1 (3.7)	0.1 mmol/kg (0.2 ml/kg)
	Gadobutrol	Gadovist® (Bayer)	18 h at 37°C	21.8 (14.7)	Kidney	1.8h	5.2 (5)	0.1 mmol/kg (0.1ml/kg)
	Gadopiclenol	Vueway® (Bracco) Elucirem® (Guerbet)	20 days at 37°C	18.7 (15.5)	Kidney	1.5h	12.2 (11.3)	0.05 mmol/kg (=0.1ml/kg)
	Gadoquatrane	Bayer (Phase III)	21 days at 37°C		Kidney		11.8 (10.5)	0.04 mmol/kg

Renal function laboratory testing Recommended but not Mandatory

During lactation: discontinuation of breast feeding for 24h (suggestion)

Evolution in UE since 2017: Recommendations of Radiological societies

- ESUR: European society of urogenital radiology
- French Radiological Society (CIRTACI)
- →
- About Macrocyclic and linear liver specific GBCAs
  - No risk of NSF even in case of renal impairment[1]
  - No nephrotoxicity
  - →No need of systematic renal function screening
  - Renal function screening if
    - Risk factors of RI + necessity of repeated injections
  - → if eGFR <30ml/min/1.73m2: interval of 7 days
  - → if eGFR >30ml/min/1.73m2: no restriction
- No discontinuation of breast feeding

1. Woolen SA et al. Risk of NSF in patient with stage 4 or 5 chronic kidney disease receiving a group II GBCA: a systematic review and meta-analysis. JAMA internal medicine 2020;180:223-230

When to use contrast?

- When NOT to use contrast?
  - In the case of repeated follow-up where the assessment of the size variation of a lesion is sufficient
  - When you get the answer before contrast injection
  - For the initial assessment of rectal cancer, contrast injection is not recommended. For restaging or follow-up in a "wait and watch" strategy, the use of GBCAs does not show a clear advantage and remains at the discretion of the radiologist

When to use contrast? General use

- Macrocyclic GBCA :
  - Each time we need to inject
    - Pancreatic imaging: Whether to characterize or monitor a pancreatic cystic or solid lesion
    - Splenic imaging: the characterization or monitoring of splenic lesions
    - Digestive tract: For the initial assessment and monitoring of chronic inflammatory bowel disease
    - Exploration of anal fistulas
    - Peritoneum: the characterization and assessment of the spread of peritoneal lesions

Which contrast to use for Liver MRI?

- Extracellular macrocyclics or intracellular linear GBCAs?
- For
  - Metastases detection
  - HCC diagnosis
  - Distinguish FNH from adenoma
  - Exploring biliary tree

Biliary tree

- MR HBP Cholangiography > MRCP
- biliary leakage follow- ing trauma, transplantation, or surgery

Metastases detection

- Meta-analysis on 3279 mets[1]

	Sensitivity	Specificity
Macrocyclics GBCAs	0.83	0.94
Hepatobiliary GBCAs	0.94	0.87

- Combined DWI and HBP examinations offer the best sensitivity for detecting liver metastases, especially those of small size[2]

	Sensitivity all size	Se,sitivity <1cm
DWI	0.87	0.69
HBP	0.91	0.83
Combination	0.96	0.91

1. Yitao Mao et al, diagnostic performance of MRI for colorectal metastasis. A systematic review and meta analysis. Nature research 2020:10,1969
2. Vilgrain V, Esvan M, Ronot M, et al. Ameta-analysis ofdiffusion-weighted and gadoxetic acid–enhanced MR imaging for the detection of liver metastases. Eur Radiol. 2016;26:4595–4615.

Metastases detection

- ➔ Use Hepatobiliary GBCA each time identification of all metastases is of clinical importance
    - Colonic cancer
    - Pre-liver surgery…

HCC diagnosis

- EASL : Classic radiological hallmark is
  - Arterial phase hyper enhancement (APHE)
  - Portal venous phase or delayed phase washout
  - In this case, no diagnostic value of the HBP

HCC diagnosis

- Thus, why using Liver specific GBCAs?
- Because liver specific GBCAs
  - Improve detection of small HCC (< 2cm)
  - Facilitate the diagnosis of borderlines Hepatic nodules (HGDN and Early HCC)
    - →HBP hypointense nodule without APHE
  - Usefull to predict MVI
    - Peritumoral arterial enhancement, non- smooth tumor margin, and peritumoral hypointensity on the HBP
  - Hypointense nodules without APHE are indicative of disease recurrence after HCC surgery
- Dependent on liver function
  - Severe cirrhosis → ineffectiveness of the HBP

HCC diagnosis

➔ Asia = Gadoxetic acid (hypo at HBP = WO, sensitivity++)

➔ Western Countries = Macrocyclic GBCAs (hypo at HPB = ancillary features, specificity++)

FNH vs Adenoma

- Central scar
  - Hyper T2
  - Late enhancing (= Macrocyclic GBCA)
- HBP
  - Uptake = FNH (and some HCA)
  - Non uptake = HCA

Additional diagnostic value for FNH/Adenomas?

- 90 FNH and 29 HCA*

	Conventional MRI	HBP analysis
Sensitivity all lesions	0.39	0.98
Sensitivity <3cm	0.20	0.97
Sensitivity > 3cm	0.88	1
Overall accuracy all lesion	0.54	0.98
Overall accuracy <3cm	0.38	0.98
Overall accuracy >3cm	0.91	1

*Roux M et al. Differenciating FNH from HCA : is HBP MRI using linear Gd chelates always useful? Adom Radiol 2018, 43:1670-1681

Conclusion

- Always think if GBCAs injection is really needed
- If needed : use them ! Always at minimal dose
- If indicated and only one examination in the week : non need of renal function testing
- For liver imaging :
  - Extracellular > intracellular GBCA if:
    - Liver function is significantly impaired
    - When the main purpose is to diagnose hemangioma
    - When specificity is more important than sensitivity
    - For follow-up of benign FLL
  - Intracellular > extracellular GBCA if:
    - Small benign FLL (once)
    - Liver mets before surgery (Colon, pancreas)
    - When sensitivity is more important than specificity
    - to predict MVI before, or disease recurrence after, HCC surgery
    - To look for a biliary leak after surgery

Merci

- Olivier.lucidarme@aphp.fr