

Contrast Media Safety

Barcelona, 15 September 2018



Management of Hypersensitivity Reactions to Gadolinium-Based Contrast Agents

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Introduction

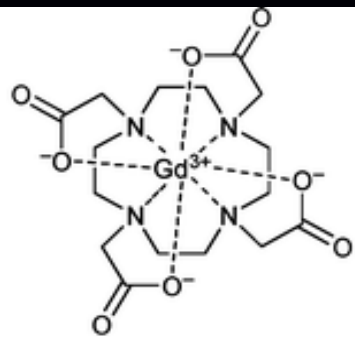
- Hypersensitivity reactions to GBCA do occur
- Older literature comprised only small series
- Since 2014 bigger series and meta-analysis published
 - > All data is retrospective, and often single center
- Management is not significantly different from ICM
- But radiologist know-how of diagnosis & treatment is poor

Hypersensitivity - WAO Terminology

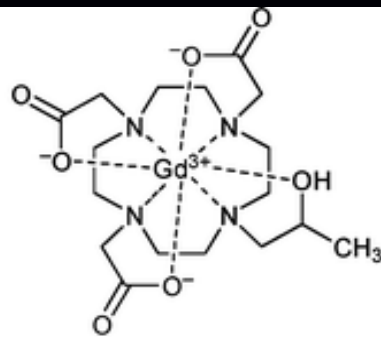
- **Drug Hypersensitivity:** Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons
- **Drug Allergy:** Drug hypersensitivity reaction with a specific immunologic mechanism; can be IgE-mediated or non-IgE (cell or IgG) mediated.
- **Anaphylaxis:** Severe, life-threatening, generalised or systemic hypersensitivity reaction. Characterised by rapidly developing life-threatening airway and/or breathing and/or circulation problems, usually associated with skin and mucosal changes

Severity of Hypersensitivity Reactions

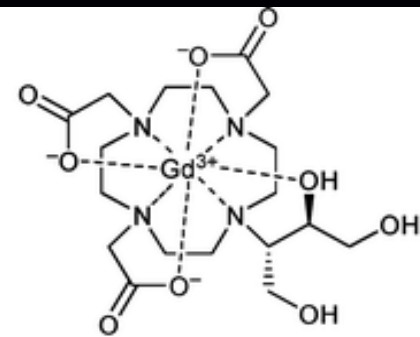
- **Minor** : dry mouth, warmth sensation, coughing, sneezing, pruritus, flushing, rhinorrhea, diaphoresis, nausea, mild vomiting, headache, limited urticaria (<10)
- **Moderate** : severe vomiting, generalized urticaria, diffuse erythema, angioedema, mild bronchospasm, dyspnea, mild hypotension,
- **Severe** : severe bronchospasm, pulmonary edema, generalized anaphylactic reaction, respiratory arrest, cardiac arrhythmia, cardiac arrest, syncope, convulsions



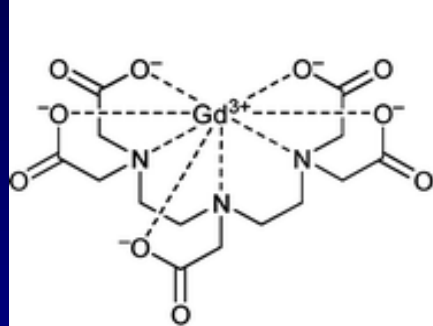
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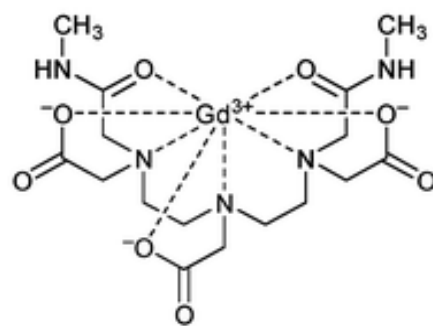
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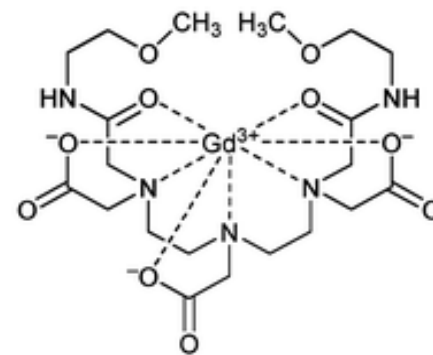
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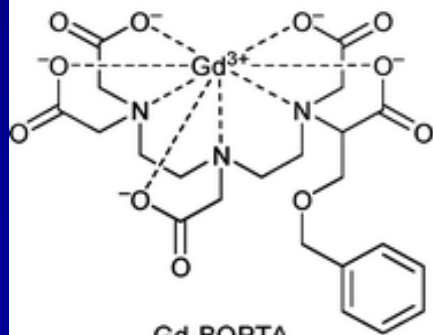
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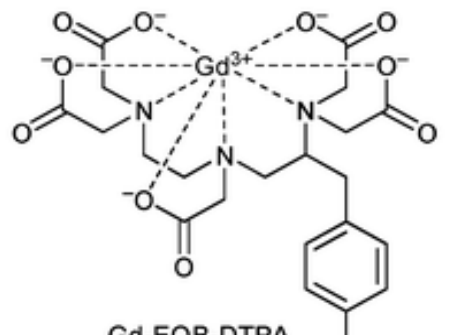
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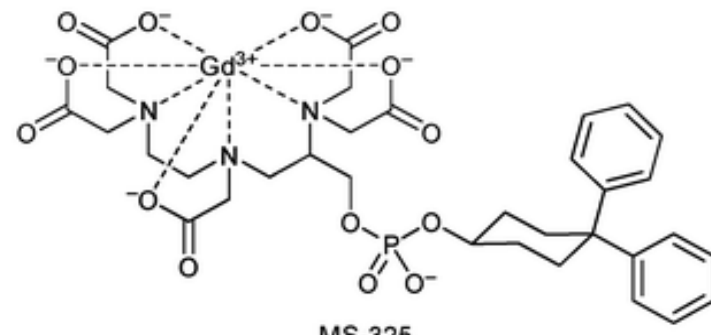
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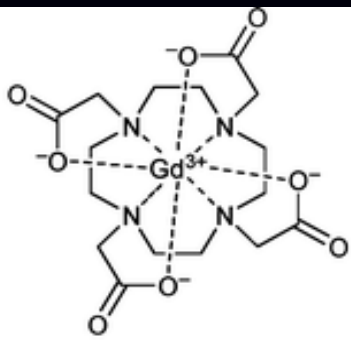
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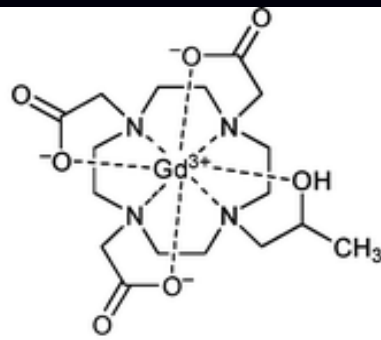
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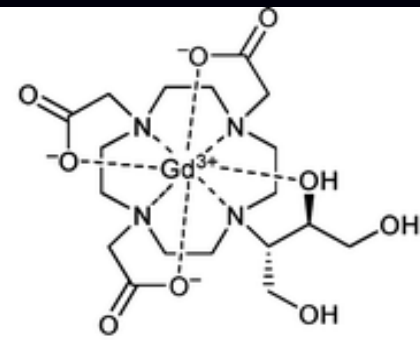
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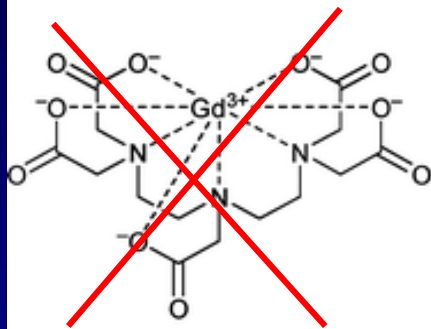
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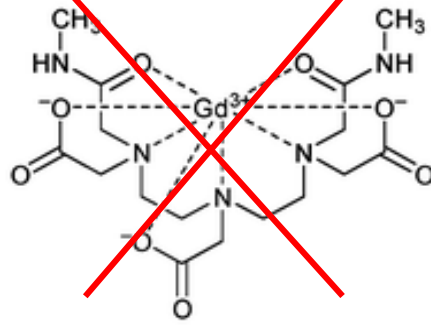
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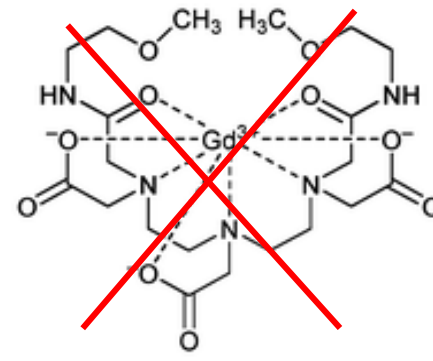
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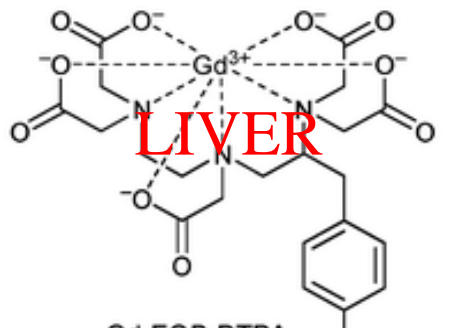
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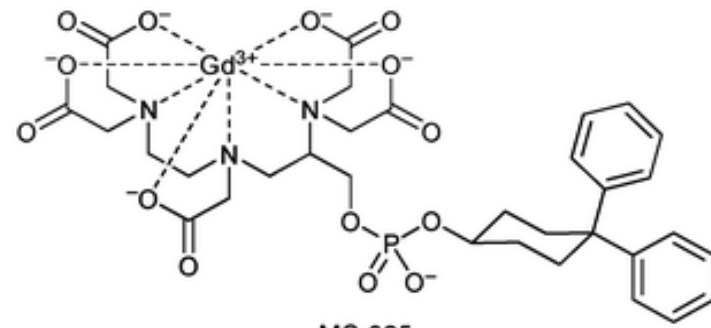
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Incidence of Immediate Gadolinium Contrast Media Reactions

- Two center, USA – 158,796 examinations
 - > Correlated to FDA AERS database
- Overall rate of reactions 94/158,796 (0,06%)
- Mild 74/94, moderate 16/94, severe 4/94 (0,003%)
- Higher frequency in: prior allergic event or reaction to GBCA, women, and abdominal exams
- Difference between GBCA: lowest for gadodiamide and most severe reactions for gadobenate

Immediate Allergic Reactions to Gadolinium-based Contrast Agents: A Systematic Review and Meta-Analysis¹

- 9 Studies – total 716,978 GBCA injections
- Overall rate 92 per 100,000 injections (0,09%)
 - > Mild 75 – Moderate 12 – Severe 5,2 per 100,000 injections
- Differences in rate among several GBCA:
 - > Linear nonionic: 15 per 100,000
 - > Linear ionic, non-protein binding: 52 per 100,000
 - > Macrocyclic ionic: 90 per 100,000
 - > Macrocyclic nonionic: 160 per 100,000
 - > Linear ionic, protein binding: 170 per 100,000

Adverse allergic reactions to linear ionic gadolinium-based contrast agents: experience with 194,400 injections

S. Aran, K.W. Shaqdan, H.H. Abujudeh*

- Single centre, USA – 4 linear ionic GBCA
- Total reactions: 204/194,400 (0.10%)
 - > Higher in gadofosveset (0.80%) and gadoxetate (0.31%)
- Most reactions mild 171/204 (83.8%)
 - > 28 moderate reactions (13.7%)
 - > 5 severe reactions (2.4% = 0.003% of total)
- More frequent in females, thoraco-abdominal MRI

2015 Update on Acute Adverse Reactions to Gadolinium based Contrast Agents in Cardiovascular MR. Large Multi-National and Multi-Ethnic Population Experience With 37788 Patients From the EuroCMR Registry

O. Bruder¹, S. Schneider², G. Pilz³, A.C. van Rossum⁴, J. Schwitter⁵, D. Nothnagel⁶, M. Lombardi⁷, S. Buss⁸, A. Wagner⁹, S. Petersen¹⁰, S. Greulich¹², C. Jensen¹, E. Nagel¹¹, U. Sechtem¹² and H. Mahrholdt^{12*}

- EuroCMR registry – 37,788 patients cardiovascular MRI
- Average dose 24,7 ml (0,12 mmol/kg)
- Overall reactions: 45/37,788 (0,12%)
 - > Mild reactions in 43 (96%)
 - > Rashes, hives, flushes most frequent
- Difference incidence between GBCA: 0,05-0,42%
 - > Lowest gadodiamide, gadobutrol, and gadoterate

Allergic-like Reactions to the MR Imaging Contrast Agent

Gadobutrol: A Prospective Study of 32 991 Consecutive Injections¹

- Single center, Canada – 32,991 injections
 - > Vast majority with gadobutrol
- Frequency reactions gadobutrol 96/30,373 (0,32%)
 - > Mild 92/96, moderate 3/96, severe 1/96 (0,003%)
 - > Break-through reactions in 12/33 (36,4%)
 - > Delayed-onset reactions in 15/96 (15,6%), all mild
- Frequency reactions gadoxetate 5/1,052 (0,48%)

Immediate Adverse Reactions to Gadolinium-Based MR Contrast Media: A Retrospective Analysis on 10,608 Examinations

- Single center, Italy – 10,608 injections
- Overall reaction rate: 32/10,688 (0,30%)
- Mild 24/32, moderate 4/32, severe 4/32 (0,04%)
- Differences in rate between GBCA
 - > Gadobenate slightly higher 0,50% and most severe reactions
- Reactions more frequent in women

Frequency and Severity of Acute Allergic-Like Reactions to Intravenously Administered Gadolinium-Based Contrast Media in Children

- Single center, USA – 32,365 exams
- Hypersensitivity reactions in 21/32,365 (0,06%)
- Mild 10/21, moderate 10/21, severe 1/21 (0,003%)
- Peak in transition between 2 GBCA (Weber effect)
- No differences between GBCA
- Group too small for meaningful risk factor analysis

Risk Factors GBCA Hypersensitivity

Rate of immediate hypersensitivity reactions is higher in:

- Patients with prior moderate-severe reaction to GBCA
- Patients with history of atopy, asthma, or drug allergies
- Women
- Thoraco-abdominal MRI ?

Rate of reactions also depends on GBCA characteristics:

- Protein-binding of GBCA
- Ionicity of GBCA
- Macrocyclic ligand of GBCA ?

Diagnosis 2018: Blood and Skin Testing

- Follow guidelines of EAACI – ENDA
- At the time of the hypersensitivity reaction:
 - > Serum Tryptase – preferably during reaction and at 2h
 - > If possible, also serum tryptase 24h
- Skin testing in center with experience in drug allergies
 - > Check of serum tryptase
 - > Skin testing needs full panel of alternative lin/mc-GBCA !
 - > Skin prick test (SP) with undiluted CM
 - > Intradermal test (IDT) with 1:10 - 1000 diluted CM

Cross-Reactivity between GBCA

- Limited data exist on GBCA cross-reactivity
 - > GBCA cross-reactivity is a rare phenomenon
- Positive SP or IDT may indicate cross-reactivity
- Generally, a negative SP and IDT results in safe administration of that specific GBCA
 - > In rare cases with hypersensitivity to mc-GBCA the only alternative would be to administer lin-GBCA

Hasdenteufel – J Allergy Clin Immunol 2008

Chiriac – Allergy 2011

Tomas – J Investig Allergol Clin Immunol 2012

Pathophysiology GBCA Hypersensitivity

- Reactions to GBCA mediated by mast cell activation
 - > Possibly also basophil activation
- Positive IDT suggests IgE mechanism in many reactions
 - > Possibly more frequent than ICM reactions
- Delayed cutaneous reactions may be T-cell mediated

Summary: Incidence Reactions to GBCA

- GBCA are in general very safe contrast media
- Overall, GBCA reactions are infrequent: 0,1-0,4%
 - > May vary with risk factors and type of GBCA
 - > Many reactions are IgE-mediated
- Severe reactions are very rare: 0,003-0,005%
- Fatalities have been described,
 - > Estimated risk in order of 0,0001%
- Cross-reactivity between GBCA is rare

For Your Practice

In a practice with 10,000 ceMRI examinations per year

- There will be 10-20 hypersensitivity reactions
 - > More if protein-binding GBCA is used
 - > 80-90% are mild, cutaneous reactions
- There will be 1 severe reaction every 2-3 years
- There may be 1 fatal reaction every 100 years

Management of GBCA Reactions

- Diagnose before you treat
- Stop administration of contrast medium directly
 - > But keep intravenous access !
- Ask history and complaint(s)
- Inspection of skin (undress !)
- Auscultation of neck and thorax
- Repetitive measurement of pulse and RR
- Liberal use of iv fluids and O₂

Management of GBCA Reactions

- Mild reactions or symptoms can be prodrome of serious reactions – can sometimes progress quickly
- Know the signs of serious CM reactions
 - > Remember ABCDE from Advanced Life Support
- Keep monitoring the patient: vital signs
- Ask for help when insecure or bad gut feeling
 - > Colleague, Internist, Rapid Intervention Team, Reanimation Team
- **Epinephrine im** is your best friend
 - > *not Antihistamines or Corticosteroids !*

Types of Hypersensitivity Reactions

- Skin & Mucosa:
 - > Urticaria, diffuse erythema, angioedema
- Respiratory:
 - > Bronchospasm, laryngeal edema, pulmonary edema
- Cardiovascular:
 - > Hypotension, generalized anaphylactic reaction, cardiac arrest

Urticaria

- Mild, scattered (< 10):
 - > No medication, keep iv access, observe for 30 min
- Moderate to severe, scattered or generalized (>10):
 - > **Clemastine (Tavegyl) 2mg slowly iv**
 - > When severe: peripheral vasodilatation
 - Active elevation legs
 - 1000ml NaCl 0.9% iv
- When extensive: risk of orthostatic hypotension
- If $RR_{sys} < 90$: **Epinephrine 0.5mg im**, repeat as necessary

Diffuse Erythema



- Skin patchy red or lobster red
- Risk of hypotension by vasodilatation
- Active elevation legs
- 1000ml NaCl 0.9% iv
- **Clemastine (Tavegyl) 2mg slowly iv**
- If hypotensive: **Epinephrine 0.5mg im**, repeat as necessary

Angioedema

- Ill-demarcated swelling of the deep soft tissues
 - > usually lips, around eyes, mucosa mouth/throat
- Risk of laryngeal edema
- 1000ml NaCl 0.9% iv
- Clemastine (Tavegyl) 2mg slowly iv
- If voice changes, hoarseness (laryngeal edema):
 - > Adrenalin 0.5mg im, repeat as necessary

Bronchospasm

- Usually patients with asthma
- Short of breath, cough, expiratory wheezing
 - > More severe if wheezing gets quieter !



- Oxygen 10 l/min by mask
- Mild: **Salbutamol (Ventolin) inhaler 2-3 deep inhalations**
 - > alternative: salbutamol (Ventolin) 0.5 mg sc
- Severe: **Epinephrine 0.5mg im**, repeat as necessary
- When protracted: add Hydrocortisone 200mg slowly iv

Laryngeal Edema

- Anxious patient, difficulty breathing
- Hoarse, soft voice, inspiratory stridor
- Oxygen 10 l/min by mask
- **Epinephrine 0.5mg im**, repeat as necessary
- When no response: **Call resuscitation team**
 - > Emergency intubation

Mild, Isolated Hypotension

- Less responsive
- Diffuse erythema or pale
 - > Systolic RR < 90 with tachycardia
- Oxygen 10 l/min by mask
- Active elevation legs
- 1000ml NaCl 0.9% iv
- Epinephrine 0.5mg im, repeat as necessary
- When not responsive: Call resuscitation team

Generalized Anaphylactic Reaction

- Components of all reaction types
- Call resuscitation team first
- Oxygen 10 l/min by mask
- Active elevation legs
- Rapid infusion 1000ml NaCl 0.9% iv (or Ringer's)
- Epinephrine 0.5mg im, repeat as necessary
 - > Titrate Epinephrine 0.025-0.05mg iv bolus **only if experienced**
 - > β -blocker: give glucagon (Glucagen) 1-5 mg slowly iv, followed by 2.5-7.5 mg iv/h for 12u **only if experienced**
- Clemastine (Tavegyl) 2mg slowly iv
- Hydrocortisone 200mg slowly iv

Vasovagal Reaction

- Warm, nausea, sweaty
- Risk of collapse
 - > Systolic RR < 90 with *bradycardia*
- Oxygen 10 l/min by mask
- Active elevation legs
- 1000ml NaCl 0.9% iv
- **Atropine 0.6-1.0 mg iv**, repeat if necessary in 0.5 mg doses
 - > Maximum dose 3.0 mg
- *Cave: Older patient on β -blocker: hypotension & bradycardia*



Drug Therapy: C.A.S.H.

Easy to Remember for Radiologists 😊

- **C**lemastine (Diphenhydramine) slowly iv
- **A**drenaline (Epinephrine) 1:1,000 im
- **S**albutamol (Albuterol) dose-aërosol inhalation
- **H**ydrocortisone slowly iv

Epinephrine (1:1,000) IM

- MOST important drug in therapy of anaphylaxis
 - > α -agonist: decreases edema, peripheral VC, increase RR
 - > β -agonist: bronchodilatation, inotropy, \downarrow histamine
- Milder Anaphylaxis: 0.2–0.5 mg im, if needed repeat every 5–15 min, max 1.0 mg per dose
- Anaphylactic Reaction: 0.5 mg im, if needed repeat every 5–15 min. In experienced hands and with ECG monitoring follow by 0.025–0.05 mg Epinephrine iv

Epinephrine Auto-Injector



- EpiPen – epinephrine 0.3 mg = 0.3 ml im
- EpiPen Junior – epinephrine 0.15 mg = 0.3 ml im
 - > Lower dose than in most guidelines
 - > Can be repeated (give 2)
- Injection anterolaterally in thigh
- Can be given through clothing
- Protected needle
- Hold 10 sec
- Massage 10 sec

TOEDIENING EIPEN®		NA TOEDIENING EIPEN®	
1. Verwijder de blauwe veiligheidsdop van de EpiPen®	2. Stoot het oranje uiteinde van de EpiPen® in één beweging stevig tegen het dijbeen. Je hoort dan een klik. Houd dit vast voor 10 seconden.	3. Verwijder de EpiPen® en wrijf de plek 10 seconden.	4. Bel 112 en meld een geval van anafylaxie. Dien een 2 ^e EpiPen® toe als de klachten binnen 5-15 minuten niet zijn verminderd.
			

Errors of epinephrine administration during severe allergic-like contrast reactions: lessons learned from a bi-institutional study using high-fidelity simulation testing

Carolyn L. Wang,¹ Matthew S. Davenport,² Sankar Chinnugounder,¹
Jennifer G. Schopp,³ Kimia Kani,¹ Sadaf Zaidi,¹ Dan S. Hippe,¹ Angelisa M. Paladin,¹
Neeraj Lalwani,¹ Puneet Bhargava,⁴ William H. Bush¹

- 58% made mistakes in epinephrine administration
 - > Use of epinephrine as first line for *mild* bronchospasm
 - > Administer epinephrine without saline IV or saline flush
 - > Overdose epinephrine via IM route
 - > Administer epinephrine 1:1,000 via IV route (!)

Clemastine (Tavegyl) iv

- H₁-receptor antagonist with long action of 12 h
 - > H1 + H2-antihistamines no advantage, only theoretical
- Administer Clemastine *very slowly* iv (1-2 min)
 - > Can be 1:5 diluted with NaCl 0.9% or glucose 5%
- Dose: 2 mg iv, can be repeated after 15 min
- *Use of this drug will lead to drowsiness with reduced reactivity and concentration. Daily activities (e.g. driving) can be hindered. NO CAR DRIVING*

Salbutamol (Ventolin) dose aërosol

- Selective β_2 -sympaticomimetic drug
 - > Bronchial dilatation, relaxation of smooth muscle
- 2-3 deep inhalations dose aërosol
 - Per inhalation 100 mcg dose aërosol
- If need repeat every 5-15 min
- Alternative: Ventolin 0.5 mg sc (0.5 mg = 1 ml)

Hydrocortisone

- Specific action: receptor binding and cytokine formation
 - > Slow action: effect starts after > 6h (premedication)
- Aspecific action: membrane stabilisation
 - > High concentration - effect in 10-30 min (acute reactions)
- Prevention of *biphasic or protracted* (respiratory) reactions
 - > Slowly: 200mg HC in 100ml NaCl 0.9% in 10 min iv
- Hydrocortisone 200mg (Solu-Cortef) equals:
 - > Prednisolone 50 mg (Di-Adreson-F)
 - > Methylprednisolone 40 mg (Solu-Medrol)
 - > Dexamethasone 8 mg (Oradexon)

Documentation

- Documentation in radiology report & RIS:
 - > Type and dose contrast medium
 - > Symptoms and progression
 - > Instituted therapy and result
 - > Preferably short term (telephonic) follow-up
 - > Advice on prophylaxis for future
- ESUR: only moderate to severe reactions need to be registered in the complication registry
- Report **severe** adverse events to CM also to your National Pharmacovigilance Institute

Better Equipped Personnel

- Update protocol CM Hypersensitivity/Anaphylaxis
- Train all Radiology staff (residents first) regularly
 - > High-fidelity simulation training best
- New visual helps e.g. posters CM reactions
 - > Separate posters for adults & children

LUMC Protocol Adults

