

PREMEDICATION FOR CONTRAST REACTIONS

MUCH ADO ABOUT WHAT EXACTLY?
A BRIEF OVERVIEW AND ANALYSIS

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Conflict of interest

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The so-called “allergy to iodine” and the premedication controversy

IODINE IS NOT CONTRAST

- Iodine is indispensable for human development
- Fish and shellfish allergy is not a risk factor. Allergens responsible are parvalbumins and tropomyosins; both are muscle proteins
- Reaction to topical iodine is unrelated to IV contrast; causative agents are compounds within the disinfectant solution and not to the iodine molecule itself

TOWARDS NEW TERMINOLOGY

- **Hypersensitivity to contrast** should be used instead
- Specifying whether reaction was immediate or delayed
- Per the World Allergy Organization:
 - *Hypersensitivity* should be used to describe objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons
 - *Allergy* is a hypersensitivity reaction initiated by specific immunologic mechanisms

WHY THE CONTROVERSY?

- Premedication protocols were created especially for hyperosmolar contrast media (HOEM), which are no longer in use
- No level 1 evidence to support its use for low/iso-osmolar iodinated contrast media (LOEM)
- Never tested for gadolinium
- Does not prevent breakthrough reactions

Historical perspective

HOCM

- Contrast media have been in use since the 1920s
- Initially, only HOCM available for clinical use
- Associated with a **5-15%** risk of significant adverse reactions
 - hypotension, cardiac arrhythmias and fluid overload
- Hence the necessity to develop some kind of premedication (Lasser and Greenberger preps)



GREENBERGER PREP

3 doses of oral corticosteroid
q 6h prior to contrast administration

WITH an antihistamine



LASSER PREP

2 doses of oral corticosteroid
the night prior and the morning
of contrast administration

WITHOUT an antihistamine

LOCM

- LOCM was developed in 1960s by Dr. Torsten Almén, a Swedish radiologist
- LOCM less toxic and better tolerated by patients
- But was 12-15 times more expensive than HOCM. Estimated increased expenditure of 1.2 billion USD in 1988 if they were to completely replace HOCM

CURRENT WIDESPREAD USE OF LOCM

- **Acute reactions occur in about 0.4% of all exposures to iodinated contrast material**

The studies

FOR HOCCM

Greenberger et al. 1981

Prospective non-randomized, non-controlled

- N = 284 pts: total of 318 C+
- Pts w/ prior **allergic-like** reactions to HOCCM

- **Oral corticosteroid q 6h up to 3 doses**
- **Antihistamine x 1 IM**

Results

- Only 24 breakthrough reactions

Conclusion

- Protocol was effective in preventing allergic-like reactions

Limits:

- No control group, no statistical analysis and no bias analysis

Lasser et al. 1987

Multi-institutional randomized controlled trial, blinded (US & CAN)

- Not all pts had a history of allergic-like reaction to HOCCM
- N = 6763 patients

- **Group 1:**
Methylprednisolone PO x 1 hs and x 1 PO morning of C+
- **Group 2:**
Methylprednisolone PO x 1, at least 2 hours before C+
- **Groups 3 and 4 :**
control groups for above, placebo treatment

Results:

- Observed rates of reactions decreased with 2 dose

Conclusion:

- The 2-dose regimen had a protective effect against all adverse reactions (p-value < 0.0001)

Limits:

- Patients with prior serious adverse reaction to HOCCM excluded
- Not significant for grade II (moderate) reactions (p = 0.06)

FOR LOCCM

Greenberger & Patterson 1991

Prospective non-randomized non-controlled

- N = 191 patients: total of 200 C+
- Pts w/ prior **allergic-like** reactions to **HOCCM**

- **Same prep**

Results:

- Only 1 breakthrough in LOCCM group (p<0.001)
- Used the data to compare to HOCCM + premedication

Conclusion

- LOCCM should be used instead of HOCCM
- "Patients should receive prednisone-diphenhydramine-ephedrine or prednisone-diphenhydramine prophylaxis

Lasser et al. 1987

3 institutions, randomized controlled trial, blinded (US only)

N = 1155 pts; 107 w/ history of contrast reaction

- N = 580 : methylprednisolone prep
- N = 575 : placebo pre-treatment

Results:

- Total of 38 pts had adverse reaction (10 in treatment arm) corticosteroids
- Premedication conferred protection against overall reactions (p<0.0001) and Grade I reactions (p<0.004)

Conclusion:

- The use of two doses of oral corticosteroids reduces overall prevalence of reactions

Limits:

- No statistical significance for Grades II (p=0.63) and III (p=0.11)
- Unclear incidence of breakthrough reactions

The game changer study

Katamaya et al. 1990

Nation-wide comparative clinical study in Japan at time of introduction of LOCM into the country

- To compare incidence of adverse reactions (AR) of HOCM vs LOCM

Population: 337 647 cases

- 50.1% received HOCM (ionic)
- 49.9% received LOCM (non-ionic)

Results:

- AR: HOCM 12.66% vs. LOCM 3.13% ($p < 0.01$)
- Less very severe ARs in non-ionic group
Such as dyspnea, sudden hypotension, cardiac arrest, and loss of consciousness
Prevalence of 0.004% ($p < 0.01$)
- Patients w/ prior contrast reactions: All AR and severe reactions were significantly lower in non-ionic group

Limits:

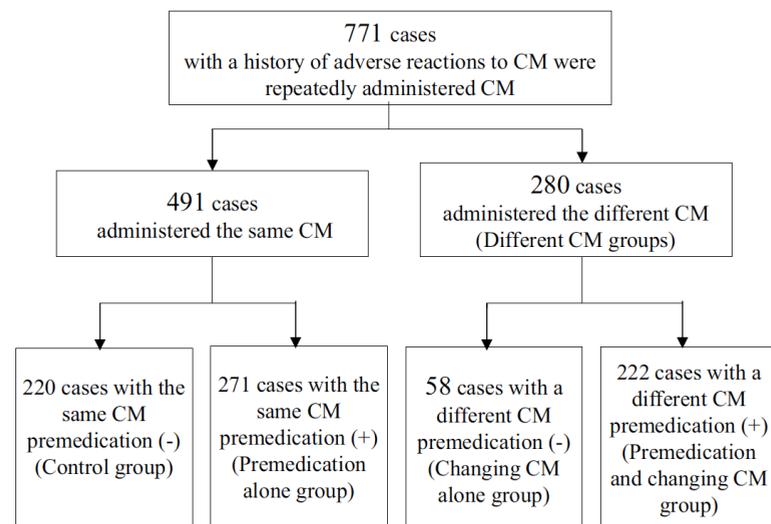
- Premedication given to patients w/ history of allergies, showed no positive effect in nonionic group
- Premedication does not seem to have been given to those with prior AR to contrast
- Incidence of breakthrough reactions unclear

Demonstrates the superior safety profile and better tolerance of LOCM over HOCM.

Thus, simply switching to LOCM reduced adverse reactions.

What about switching contrast?

Study performed by Ab et al. (2015) with LOCM



GROUP	REPEAT REACTION
Control: same contrast, no premedication	27.7%
Same contrast, with premedication	17.3%
Changing contrast, NO PREMEDIATION	5.2% ($p < 0.001$)

Using a different contrast than the causative agent may be more effective than premedication alone

What about the urgent IV premedication protocols?

Greenberger et al. 1986	Mervak et al. 2017
<p>10 patients h/o anaphylactoid reaction to contrast Undergoing urgent procedure with contrast Presumed HOCM (not specified in study)</p> <p>Premedication protocol :</p> <ul style="list-style-type: none">• Not standardized across 10 patients• 1, 2 or 3 doses Hydrocortisone 100 – 250 mg IV anywhere between 9h and 1h before contrast• + Diphenhydramine 50mg PO or IV, between 1-2h prior• 1 patient also received ephedrine 25 mg PO <p>Conclusion:</p> <ul style="list-style-type: none">• No patients reacted adversely to re-exposure to RCM <p>This premedication protocol was the only one recommended by the ACR, until 2016.</p> <p><u>Based on a study of n = 10 using HOCM</u></p>	<p>Non-inferiority study to determine if breakthrough reaction rate is non inferior with 5h IV regimen vs. 13h oral regimen. IV = 202 patients ; oral = 626 patients</p> <p>Breakthrough rate: 2.5% for IV and 2.1% for oral (P = 0.0181).</p> <p>Conclusion:</p> <ul style="list-style-type: none">• The 5-hour IV premedication protocol has a similar efficacy in preventing breakthrough reaction• “Neither regimen prevented all moderate and severe breakthrough reactions, and breakthrough reactions usually were of equivalent or lesser severity than were index reactions.”

“ The multihour length of the premedication schedule is based on the pharmacology of corticosteroids requiring 4 to 6 hours or more to achieve efficacy ”

Davenport & Cohan (2017)

“Minimizing the duration of prophylaxis is advantageous to accelerate diagnosis in emergent situation. (...) there is a minimum duration below which corticosteroids are ineffective in reducing the incidence of reactions to [radiocontrast media]”

Mervak et. al (2017)

Point of view of Allergy Specialist: Dr. Matthieu Picard

Reaction to HOCM

- Most patients with a past reaction to a HOCM will tolerate any LOCM **without premedication**.
- Allergy referral can be considered if:
 - Patients reluctant to receive LOCM despite adequate reassurance
 - Patients in whom the use of premedication is problematic and who are reluctant to receive LOCM without premedication

Immediate reaction to LOCM

- Most patients will **tolerate a different LOCM**
- Thus, it is paramount to **document the name** of the contrast agent used. Rapid access to at least 3 different LOCM is important
- Patterns of reaction and cross-reactivity may vary depending on which contrasts are used in the community.
- Most reactions in Qc are to omnipaque (iohexol). The majority of patients reactive to omnipaque (iohexol) will tolerate isovue (iopamidol)
- Allergy referral is strongly encouraged for any severe immediate reaction to LOCM.
- For benign reactions, if access to allergist is difficult, could consider **using a different LOCM** that usually does not cross-react, **without premedication**.

Delayed reaction to LOCM

- Premedication regimens do **not usually prevent this type of reaction** (especially severe reactions eg: diffuse pruritic skin eruptions)
- Allergy referral is especially useful in patients with a past severe delayed reaction.
- If the past reaction was not severe and allergy referral is not easily accessible, one could try re-exposure with a different LOCM that usually does not cross-react.

Immediate reaction to Gadolinium

- All the premedication studies were undertaken for iodinated contrast media, **effectiveness of premedication for gadolinium is unknown**.
- Most patients will tolerate a different gadolinium agent
- **Documentation of the name** of the agent used is thus very important. Rapid access to at least 3 different gadolinium-based agents is important
- Most reactions in Qc are to: multihance (gadobenate dimeglumine) or prohance (gadoteridol)
- Allergy referral is strongly encouraged for any severe immediate reaction.
- For benign reactions, if access to allergist is difficult, could consider **using a different gadolinium agent, without premedication**.

So what should the Radiologist do?

1

Continue using premedication in patients who tolerate it well and who prefer this option.

2

Offer premedication to patients with a prior immediate reaction to a HOCM who would otherwise refuse LOCM.

3

For patients with a prior benign reaction to LOCM or gadolinium: use a different agent that usually does not cross-react, without premedication.

4

For patients with a prior severe reaction to LOCM or gadolinium: consider Allergy referral before re-exposure

TAKE-HOME MESSAGE

“Hypersensitivity to contrast” should be used. Immediate or delayed reaction should be documented.

“Allergy to iodine” is a misnomer

NO LEVEL 1 evidence supporting premedication regimens

Switching contrast may be more effective

DO NOT premedicate patients with history of **delayed reactions** to contrast.

Effectiveness of premedication for gadolinium is unknown.

Consider advice from Allergy Specialist

Refer to Allergy Specialist:

1. History of severe immediate or delayed reaction to LOCM or gadolinium
2. Breakthrough reaction despite premedication
3. Patient reluctant to withdraw premedication and premedication problematic
4. Patient reluctant to receive any contrast because of past reaction and despite adequate reassurance

Premedication does not protect against breakthrough reactions delayed reactions, nor moderate to severe reactions in high-risk patients.

Radiologists must be cognizant of this fact so to always be well prepared.

Urgent IV premedication protocols starting < 5h before contrast exposure have not been studied nor validated.

Original IV premedication protocol based on case series of 10 patients (1986)