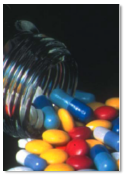
XXII World Allergy Congress

Adverse reactions to NSAIDs

Desensitization

***Prof* Pascal DEMOLY**
Division of Allergy
University Hospital of **Montpellier**
INSERM U657
France



DESENSITIZATION IN NSAID HS

DEFINITION

Desensitization or tolerance induction

- Drug desensitization is defined as the **induction of a temporary state of tolerance** of a compound responsible for a hypersensitivity reaction
- It is done by administering increasing doses of the medication concerned over a short period of time *(from several hours to a few days)*, until the total cumulative therapeutic dose is achieved and tolerated

Cernadas JR, ENDA/EAACI Allergy 2010

Desensitization or tolerance induction

- Mainly performed in IgE-mediated reactions: *immediate allergic drug hypersensitivities*
- Also, in reactions where drug-specific IgE have not been demonstrated: *both immediate and non-immediate non-allergic drug hypersensitivities*
- Never in patch test + / late reading ID test + patients: *non immediate allergic drug hypersensitivities*
  (but in an allopurinol induced FDE case report - a type IV allergy)

Cernadas JR, ENDA/EAACI Allergy 2010

Drug provocation vs Desensitization

	Drug provocation	Desensitization
Hypersensitivity	Unproven	Proven
Intention	Confirm or disprove hypersensitivity	Produce temporal tolerance
Effect on immune system	None	Tolerance
Risk of allergic reactions	Present	Present
Initial dose	1/100-1/10 of therapeutic dose	1/1,000,000-1/10,000 of therapeutic dose
Number of steps	Normally 3-5	Normally >10
Time interval between doses	According to reaction	15 minutes to 2 hours
Action after objective reaction	Discontinue test, treat patient	Stop, treat when needed, continue procedure after symptoms resolve, consider modification of protocol

Cernadas JR, ENDA/EAACI Allergy 2010

DESENSITIZATION IN NSAID HS

PREREQUISITES

What are the indications, precautions?

- Proven drug hypersensitivity and no satisfactory alternatives
- Without any contra-indications (severe clinical forms)
- Away from initial reaction
- Patients informed and ready to be followed up closely and to treat through any adverse reactions
- Under hospital surveillance
- *No other drugs introduced during 6 weeks*

Successful protocols in literature

Type of drug	Drugs
Antibiotics	Penicillins, Cephalosporins Aminoglycosides, Quinolones Vancomycin, Sulfonamides Anti-tuberculous agents Pentamidine, anti-HIV drugs
Other agents	**Aspirin, NSAIDs** Chemotherapeutics Biologicals (Measles vaccine, Tetanus toxoid, Monoclonal Abs) Desferoxamine, D-penicillamine Allopurinol Corticotropin Heparin, Insulin

Cernadas JR, ENDA/EAACI Allergy 2010

Desensitization or tolerance induction

- Mainly performed in IgE-mediated reactions: *immediate allergic drug hypersensitivities*
- Also, in reactions where drug-specific IgE have not been demonstrated: *both immediate and non-immediate non-allergic drug hypersensitivities*

  = Acute cross-reactive types of NSAID HS
- Never in patch test + / late reading ID test + patients: *non immediate allergic drug hypersensitivities*

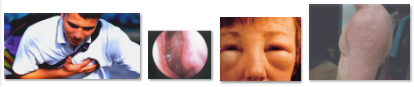
Cernadas JR, ENDA/EAACI Allergy 2010
Kowalski ML, ENDA/EAACI Allergy 2011

DESENSITIZATION IN NSAID HS

PROTOCOLS

Types of reactions to ASA and other NSAIDs

Type	Reaction	Underlying Risk Factor	Cross-Reactions to Other NSAIDs	First Exposure Reaction	Mechanism of Sensitivity	Able to Undergo Desensitization
I	NSAID-induced rhinitis and asthma	Asthma, nasal polyps, sinusitis	Yes	Yes	COX-1 inhibition	Yes
II	NSAID-induced urticaria/angioedema	Chronic idiopathic urticaria	Yes	Yes	COX-1 inhibition	No
III	NSAID-induced urticaria/angioedema	None	Yes	Yes	COX-1 inhibition	Yes
IV	NSAID-induced urticaria/angioedema	None	No	No	Immunologic*	Yes
V	NSAID-induced anaphylaxis	None	No	No	Immunologic*	Yes



Gollapudi RR et al. JAMA 2004

Types of reactions to ASA and other NSAIDs

Timing of reaction	Clinical manifestation	Type of reaction	Underlying disease	Putative mechanism
Acute (immediate to several hours after exposure)	Rhinitis/asthma	Cross-reactive	Asthma/rhinosinusitis/ nasal polyps	Inhibition of COX-1
	Urticaria/angioedema	Cross-reactive	Chronic urticaria	Inhibition of COX-1
	Urticaria/angioedema	Multiple NSAIDs-induced	No underlying chronic disease (in some patients, the reaction to NSAIDs may precede development of chronic urticaria)	Unknown Presumably related to COX-1 inhibition
	Urticaria/angioedema/ anaphylaxis	Single drug-induced	Atopy Food allergy Drug allergy	IgE-mediated
Delayed (more than 24 h after exposure)	Fixed drug eruptions. Severe bullous skin reaction Maculopapular drug eruptions Pneumonitis Aseptic meningitis Nephritis Contact and photocontact dermatitis	Single drug or multiple drug-induced	Usually no	T-cell-mediated (Type IV) Cytotoxic T cells NK cells Other

DS documented

DS poorly documented

DS not documented

Kowalski ML, ENDA/EAACI Allergy 2011

Aspirin desensitization *(1)*

- Progressive administration, over a few hours of increasing doses of ASA:
  - 30/60/100/300/600 every 2 hrs *(Nasser AJRCCM 1995)*
  - 30/60/100/150/250/500 every 3 hrs *(Rozsasi Allergy 2008)*
  - 1/10/20/50 every 30 min *(Pur RFA 2009)*
- Uses the refractory period after a reaction:
  - described at the beginning *(Widal Presse Med 1922)*
  - lasts 2-5 days, lost at day 7 *(Pleskow JACI 1982)*
  - extended to other NSAIDs

Aspirin desensitization *(2)*

- For which benefit?
  - **Improve asthma** *(Stevenson JACI 1996)*
    - 600-1200 mg/dy --> frequent gastrointestinal problems
    - still controversal
  - **Improve nasal polyposis** *(Rozsasi Allergy 2008)*
    - 300 mg/dy --> no relapse (100 mg/dy=placebo) at 27 mths
    - no large series
  - **As antiplatelet drug:**
    - ischemic cardiopathy: 75 mg/dy *(Silberman Am J Cardiol 2005)*
    - ischemic stroke: 150 mg/dy
    - abortion in antiphospholipid syndrom: 75 mg/dy

DESENSITIZATION IN NSAID HS

CONCLUSION

EAACI

Need for protocols

- ✓ **Tolerance inductions seem to work**
- ✓ **Many protocols exist,** *as many different protocols as leading teams*
- ✓ **In small case series, involving mostly patients with the acute cross-reactive type of NSAID hypersensitivity**
- ✓ **Mostly for aspirin, and cardiovascular indications**
- ✓ **We need to share and evaluate our protocols in larger case series**