Drug Hypersensitivity - Classification by mechanism

Oliver HAUSMANN
Department of Rheumatology, Immunology and Allergology, Inselspital Bern

ADR-AC GmbH Bern

Löwenpraxis Luzern
Switzerland
Disclosure

In relation to this presentation, I declare that there are no conflicts of interest.

A conflict of interest is any situation in which a speaker or immediate family members have interests, and those may cause a conflict with the current presentation. Conflicts of interest do not preclude the delivery of the talk, but should be explicitly declared. These may include financial interests (eg. owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.
Classification adverse events

**Adverse event:** medical events regardless of causal relationship to drug

**Adverse drug event:** harm caused by the drug (± medication error)

**Adverse drug reaction (type A and B):** noxious response to a drug which is unintended

**Type B reaction (mainly hypersensitivity):** only susceptible individuals

O’Hehir RE, Holgate ST, Sheikh A. Middleton’s Essential Allergy, 1st Edition 2015
Classification ADR type A and B
pharmacology

- Drug-drug interaction
- Overdosing
- Toxicity (renal, hepatic,...)
- “off-target” receptor binding
pharmacology

Predictable
Dose dependent
Rational
(mode of action)

immunology
allergology
pharmacology
Predictable
Dose dependent
Rational
(mode of action)

immunology
allergology
Not predictable
Not dose dependent
Not rational
Bizarre
The drug is OK, just the patient is weird.
pharmacology

Predictable
Dose dependent
Rational
(mode of action)

immunology
allergology

Non-A
Allergic

Pseudo-allergic

Adaptive immune system (type I-IV)
(pro-)hapten concept
Immediate - delayed

Innate immune system (mast cell, granulocyte)
enzymes, co-factors

Adaptive immune system (type IV)
T cells, p-i concept «off-target» activity

Pharmacologic
Allergic pseudoallergic pharmacologic

Innate immune system (mast cell, granulocyte)
NSAIDs, ACE inh., fluoroquinolone

Adaptive immune system (type I-IV)
penicillin

Adaptive immune system (type IV)
Anticonvulsants, Allopurinol
Allergic

Pseudo-allergic

Adaptive immune system (type I-IV)
(pro-)hapten concept
Immediate - delayed

Innate immune system (mast cell, granulocyte)
enzymes, co-factors
NSAIDs
ACE inhibitor

Mast cell receptor MRGPRX2
Common chemical motif in fluoroquinolones, NMBA, ...

Allergic pseudo-allergic

Innate immune system (mast cell, granulocyte)
- enzymes, co-factors
- NSAIDs
- ACE inhibitor

Adaptive immune system (type I-IV)
- (pro-)hapten concept
- Immediate - delayed

Common chemical motif in fluoroquinolones, NMBA, ...

Allergic

Pseudo-allergic

Adaptive immune system (type I-IV)
(pro-)hapten concept
Immediate - delayed

Innate immune system (mast cell, granulocyte)
enzymes, co-factors

Adaptive immune system (type IV)
T cells, p-i concept
«off-target» activity

Pharmacologic
Classification by mechanism

Impact on:

• Clinical manifestation
• Dose dependence
• Predictability
• Cross-reactivity and safe alternative(s)
Classification by mechanism

Impact on:
- Clinical manifestation
- Dose dependence
- Predictability
- Cross-reactivity and safe alternative(s)

Classification by mechanism

Impact on:
- Clinical manifestation
- Dose dependence
- Predictability
- Cross-reactivity and safe alternative(s)

**p-i concept:**
- Severity
- Drug level: after up-dosing or change in drug excretion
Classification by mechanism

Impact on:
• Clinical manifestation
• Dose dependence
• Predictability
• Cross-reactivity and safe alternative(s)

p-i concept:
- Severity
- Drug level
- HLA assoc.
- Separate analysis
Predictable
Dose dependent
Rational
(mode of action)
Predictable
Dose dependent
Rational
(mode of action)

Not predictable
Not dose dependent
Not rational
Bizarre
«off target» binding to non-immune receptors

«off target» binding to immune receptors (p-i reactions)
Conclusion
Conclusion

• Distinction of type A and B reaction useful
• Type B reactions subclassification:
  – Allergic
  – Pseudoallergic
  – Pharmacological
• Type A and B reactions show overlapping features (p-i reaction)

Clues for p-i reactions:
• Severe reactions (DRESS, SJS)
• Drug properties & experience (allopurinol vs. amoxicillin)
• Known HLA-association
Conclusion

- Distinction of type A and B reaction useful
- Type B reactions subclassification:
  - Allergic
  - Pseudoallergic
  - Pharmacological
- Type A and B reactions show overlapping features (*p-i reaction*)
- Might fit for syntheticals and biologicals
- Might fit for the different specialities
THANK YOU

Werner Pichler
Antonia Bünter
Nicole Wirth
Cornelia Dängeli
Lisa Pichler

Daniel Yerly
Arthur Helbling
Clinic
Diagnosis as a combination of

- Chronology
- Mechanism
- Eliciting drug
- Symptoms
- Testing
Diagnosis as a combination of

| Chronology | immediate / delayed type |
| Mechanism   | (pseudo)allergic / pharmacological reaction to amoxicillin ... |
| Eliciting drug | - with urticaria / MPE / ... |
| Symptoms    | - based on skin / in vitro testing |
| Testing     |
Diagnosis

Clinician (bed-side) Acute urticaria and angioedema drug induced?
Diagnosis

Clinician (bed-side)  
Acute urticaria and angioedema drug induced?

Allergologist (work-up)  
immediate type allergic reaction to amoxicillin  
- with urticaria and angioedema  
- with cross-reactivity to ...  
- based on intradermal skin testing, basophil activation test (BAT) and drug provocation testing
Clinician (bed-side) maculopapular exanthema (MPE) drug induced?
Diagnosis

Clinician (bed-side)
maculopapular exanthema (MPE)
drug induced?

Allergologist (work-up)
Delayed type allergic reaction to amoxicillin
- with maculopapular exanthema
- with cross-reactivity to ...
- based on intradermal skin testing and lymphocyte transformation test (LTT)
Diagnosis

Clinician (bed-side) Acute reaction during 7th infliximab infusion
Diagnosis

Clinician (bed-side)
- Acute reaction during 7th infliximab infusion

Allergologist (work-up)
- Immediate type pseudoallergic reaction to infliximab
  - with urticaria and dyspnea
  - with mast cell involvement
  - based on negative intradermal skin testing and elevated tryptase in acute phase