Allergy and antihistamines


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These slides are from the lectures given at the Université catholique de Louvain by Prof. P Tulkens
A simple question...

How was histamine discovered?

- by chemical synthesis …
- from the analysis of plant extracts (ergot fungus *Claviceps purpurea*)
- from the analysis of animal tissues extracts
- through none of these approaches
Histamine …

- obtained by synthetic chemist in 1907 … as a chemical curiosity …
  - detection of an identical compound in an extract from ergot fungus … and shown to cause a marked vasodilatation
  - a similar effect is seen with tissues extracts
    - produces a similar picture as a very severe allergic reaction
      - recognized as a "biological" molecule (and not a product from putrefaction in 1927 …)
From histidine to histamine ...

L-histidine decarboxylase

First inhibitor of histamine action ... commercialized in France (HYPOSTAMINE ®)
Localization of histamine

1. blood
   - total blood
   - plasma
   - leucocytes
   - mastocytes

2. tissues ... the word comes from τοστος ("histos" = tissue !!)
   - skin
   - lung
   - gastrointestinal tract
   - central nervous system
Actions of histamine

- ↑ of capillary permeability and vasodilatation
  - rednesses
  - inflammation
- bronchoconstriction
  important with the guinea-pig but under H₂ retrocontrol in man
- ↑ of HCl secretion
  (parietal cells of the stomach)
- neurotransmission
  - awakening reactions, tachycardia, hypertension
  - nauseas, vomiting
  - migraines

Cutaneous signs
Neurological and comportmental signs
Rappel: les 4 types de réactions d'hypersensibilité

**Réaction de type I: anaphylactique**
- **allergène**
- **IgE**
- **mastocyte**
- libération d'amines vasoactives dont l'histamine

**Réaction de type II: cytotoxique**
- mediée par les IgG et/ou les IgM
- action directe sur une cellule cible
- implique le complément
- lyse, phagoytose (anémie hémolytique, agranulocytose, thrombopénie)
- délai: 5-12h

**Réaction de type III: formation de complexes immuns**
- dépôts dans les tissus avec réaction inflammatoire disséminée
- activation du complément et libération de toxines des leucocytes
- agrégation plaquettaire, microthromboses…
- délai: 3-8h

**Réaction de type IV : cellulaire**
- activation directe des cellules T
- libération de cytokines et de TNFα
- induit typiquement des manifestations cutanées (dermatite de contact, exanthèmes, eczema, …)
- délai: 24 à 48h
From histamine to anti-histamines ...

starting in the 40s ...

Building two aromatic rings

or get a rigidified structure with the same shape (tricyclic)

ALL H$_1$ antihistaminics
Rationalization through a deep understanding of the receptor

- $H_1$ receptor
  - CNS
  - périphery
- $H_2$ receptor
  - stomach
  - lung
  - CNS
- $H_3$ receptor
  - CNS

action mediated by the phosphoinositides

action mediated by cyclic AMP
Binding of histamine to H1 receptor

Asp 127

TM III

TM IV

TM V

TM VI

Asn 198

Phe 199

NH₂

NH₃⁺
Binding of histamine to H1 receptor

Asn 198: site for imidazole ring binding

Phe 199: hydrophobic interaction

Asp 127: binding site for bioamines

Signal transduction !!
Binding of an antagonist ...
Binding of an antagonist ...

Block !

Binding to the bioamines site

hydrophobic interaction
<table>
<thead>
<tr>
<th>Nom DCI</th>
<th>nom commercial en Belgique *</th>
</tr>
</thead>
<tbody>
<tr>
<td>alimémazine</td>
<td>THERALENE</td>
</tr>
<tr>
<td>prométhazine</td>
<td>PHENERGAN</td>
</tr>
<tr>
<td>dimenhydrinate</td>
<td>PARANAUSINE / VAGOMIN</td>
</tr>
<tr>
<td>diphenhydramine</td>
<td>BENYLIN</td>
</tr>
<tr>
<td>dexchlorphéniramine</td>
<td>POLARAMINE</td>
</tr>
<tr>
<td>ciproheptadine</td>
<td>PERIACTIN</td>
</tr>
<tr>
<td>dimétindène</td>
<td>FENISTIL</td>
</tr>
<tr>
<td>méclozine</td>
<td>AGYRAX / POSTAFENE</td>
</tr>
<tr>
<td>cetirizine</td>
<td>ZYRTEC / REACTINE / ....</td>
</tr>
<tr>
<td>loratadine</td>
<td>CLARITINE / SANELOR</td>
</tr>
<tr>
<td>fexofenadine</td>
<td>TELFAST</td>
</tr>
<tr>
<td></td>
<td>et plus récemment</td>
</tr>
<tr>
<td>lévocetirizine</td>
<td>XYZAL</td>
</tr>
<tr>
<td>desloratadine</td>
<td>AERIUS</td>
</tr>
</tbody>
</table>

* liste non limitative...
Binding of an antagonist: what can you modify?
Binding of an antagonist: what can you modify?

Not much, or very little here...
Binding of an antagonist: what can you modify?

Possibilities...
Variations among antihistamines....

Modifications of the amine pole

Dimenhydrinate
Diphenhydramine
Dexchlorphenyramine

Dialkyl

Buclizine
Meclozine
Cétirizine

Pipérazine

Loratadine
Terfenadine
Ebastine
The ideal antihistaminic drug for the treatment of allergy

What is your "wish list"?

• Low sedation activity *
• No or little anticholinergic effects **
• Getting a rapid and prolonged action ***

* most "old" antihistamines make you to fall asleep…
** because their structure is reminiscent of atropine
*** I want a fast relief, and not needing taking pills every hour…
Low sedation activity ...

Modulation of the hematoencephalic barrier passage...

Fast and important passage

Low or no passage

role of the side-chain...
Low sedation activity ...

Another example…

Important passage

Low or no passage

 rôle of the length and of the polarity of the side-chain
## Molécules à passage hémato-méningé important et causant de la sédation ...

<table>
<thead>
<tr>
<th>Nom DCI</th>
<th>sédation</th>
<th>OTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>alimémazine</td>
<td>+++</td>
<td>oui (partiel.)</td>
</tr>
<tr>
<td><strong>prométhazine</strong></td>
<td>+++</td>
<td>oui</td>
</tr>
<tr>
<td>dimenhydrinate</td>
<td>+++</td>
<td>oui</td>
</tr>
<tr>
<td>diphenhydramine</td>
<td>+++</td>
<td>oui</td>
</tr>
<tr>
<td>oxomémazine</td>
<td>++</td>
<td>non</td>
</tr>
<tr>
<td><strong>dexchlorphéniramine</strong></td>
<td>++</td>
<td>oui</td>
</tr>
<tr>
<td>ciproheptadine</td>
<td>++</td>
<td>oui</td>
</tr>
<tr>
<td>dimétindène</td>
<td>+</td>
<td>oui</td>
</tr>
<tr>
<td>méclozine</td>
<td>+</td>
<td>oui</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oui</td>
</tr>
</tbody>
</table>
The antihistaminic and the sedative actions of the "old" antihistaminics go side by side

Promethazine (PHENERGAN 30 mg)

Figure 3. Change from baseline: peripheral antihistaminic suppression (weak) with respect to CFF threshold: acute dose promethazine 30 mg, day 1

First molecules with low level of passage through the hemato-encephalic barrier

- astémisole
- terfénadine

withdrawn because of cardiac toxicity

*Torsades de pointe* !!!

- fexofénadine

Active metabolite of terfenadine
What was terfenadine...

- terfenadine was a pro-drug

- which underwent a "first pass" liver metabolism that released fexofenadine, the active product
The main problem of terfenadine ...

- if terfenadine reaches the heart, it will block the K⁺ canal, causing a delay in repolarization (that translate into a prolongation of Q-T interval [visible at the ECG] that may lead to **life-threatening** arhythmia and "**Torsades de pointes**" ...)
What is "Torsades de pointe"?

Figure 1. Initiation of torsades de pointes. Note the prolonged QT interval of the last preceding beat, the twisting polarity and the changing amplitude of the QRS complexes during the arrhythmia.
Risk of Torsade de pointes and inhibitors of cyt P450 metabolism

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>Amiodarone (with roxithromycin [23]), quinidine (with erythromycin [116]), disopyramide (with clarithromycin [117, 118])</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Fluconazole, ketoconazole, itraconazole, miconazole</td>
</tr>
<tr>
<td>Prokinetics</td>
<td>Cisapride (with clarithromycin, [119, 120], with erythromycin [121])</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Terfenadine (with erythromycin [122, 123], with troleandomycin [124]), astemizole (with erythromycin [125]), loratidine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Pimozide (with clarithromycin [126, 127]), chlorpromazine, haloperidol, ziprasidone, risperidone, clozapine, quetiapine</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Opioid agonists</td>
<td>Methadone</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Quinine, chloroquine, halofantrine</td>
</tr>
</tbody>
</table>

Case reports on torsades de pointes or QT prolongation during coadministration of macrolide agents and other repolarization prolonging drugs are in brackets

Simkó et al., Infection 2008;36:194-206
Molecules with a weak hemato-encephalic passage ...

- **loratadine**
  - must be metabolized into desloratadine

- **ebastin**

- **cetirizine**
  - not very sedative and acting as such
Dissociation of the antiallergic and sedative activities

Figure 5. Change from baseline: peripheral antihistaminic suppression (weal) with respect to CFF threshold: acute dose cetirizine 10 mg, day 1

Dissociation of anti-allergic and sédative activities...

But, **beware:**

This is all related to dose…
Dissociation of anti-allergic and sedative activities…

Everything is related to dose…


antiallergic activity

placebo  cetirizine

-60 -40 -20 0 20 40 60 % from baseline

sedative activity

placebo  cetirizine

0 5 10 % from baseline

10 mg  20 mg

10 mg  20 mg
The ideal anti-H1 drug for treating allergy...

Specifications *(Cahier de charges)*

- Low sedative potential
- **Avoiding anti-cholinergic effects**...
  - important for old molecules
    - *(Hydroxyzine, diphenhydramine, prométhazine, cyproheptadine, méquitazine, dexchlorphéniramine, alimémazine)*
      ➔ sight troubles, urinary retention ...
  - much improved for new ones
    - *(loratadine, fexofénadine, cétirizine)*
- Getting a rapid and sustained action
The ideal anti-H1 drug for treating allergy...

**Specifications** *(Cahier de charges)*

- Low sedative potential
- Avoiding anticholinergic effects
- **Getting a fast and sustained action**
Moelcular properties of cetirizine

- fast action because no necessity of metabolic activation
  (网通 terfenadine, loratadine…)
- little of no penetration through the blood-brain barrier
- **long occupation of the receptor …**
Binding of an H\textsubscript{1} antagonist to the receptor...

Presence of a lysine in position 191

Slow release of an antagonist ...

Slow dissociation and long-lasting action

Prolonged action ...

**Figure 5.** Change from baseline: peripheral antihistaminic suppression (weal) with respect to CFF threshold: acute dose cetirizine 10 mg, day 1

Cetirizine and levocetirizine...

Acetic acid, 2-[2-4-[(R)-(4-chlorophenyl)phenylmethyl]-1-piperazinyloxy]-
Sur base de ce que vous avez appris jusqu'ici, quel est, à votre avis, le conseil le plus essentiel à donner au patient lors de la délivrance d'un antihistaminique de type cétérizine, loratadine ...

- faire attention aux autres médicaments
- ne pas abuser du produit
  (ne pas reprendre trop rapidement)
- attention à l'alcool !
- respecter la posologie
- attention à la somnolence