

A simple question...

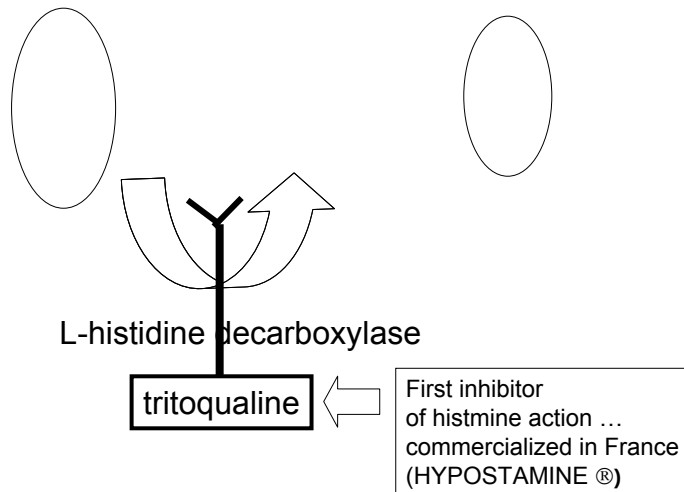
How was histamine discovered ?

- 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 ...

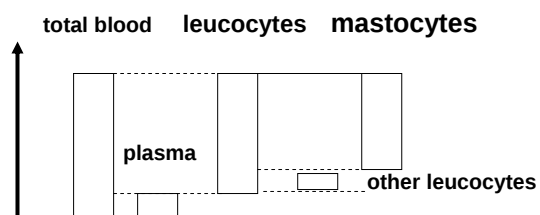
- ➔ obtained by synthetic chemist in 1907 ...as a chemical curiosity ...
 - detection of an identical compound in an extract from ergot fungus ... and shown to cause a marked vasodilatation
 - a similar effect is seen with tissues extracts
 - produces a similar picture as a very severe allergic reaction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

From histidine to histamine ...



Localization of histamine

1. blood

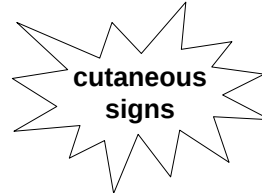


2. tissues ... the word comes from ιστος ("histos" = tissue !!)

- skin
- lung
- gastrointestinal tract
- central nervous system

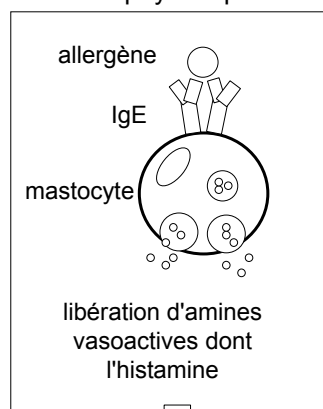
Actions of histamine

- **↑ of capillary permeability and vasodilatation**
 - rednesses
 - inflammation
- bronchoconstriction
 - important with the guinea-pig but under H_2 retrocontrol in man
- **↑ of HCl secretion**
 - (parietal cells of the stomach)
- **neurotransmission**
 - awakening reactions, tachycardia, hypertension
 - nausea, vomiting
 - migraines



Rappel: les 4 types de réactions d'hypersensibilité

Réaction de type I anaphylactique



- rhinite, conjonctivite, urticaire, asthme aigu, (bronchospasme), oedème
- délai: endéans les 30 min

Réaction de type II: cytotoxique

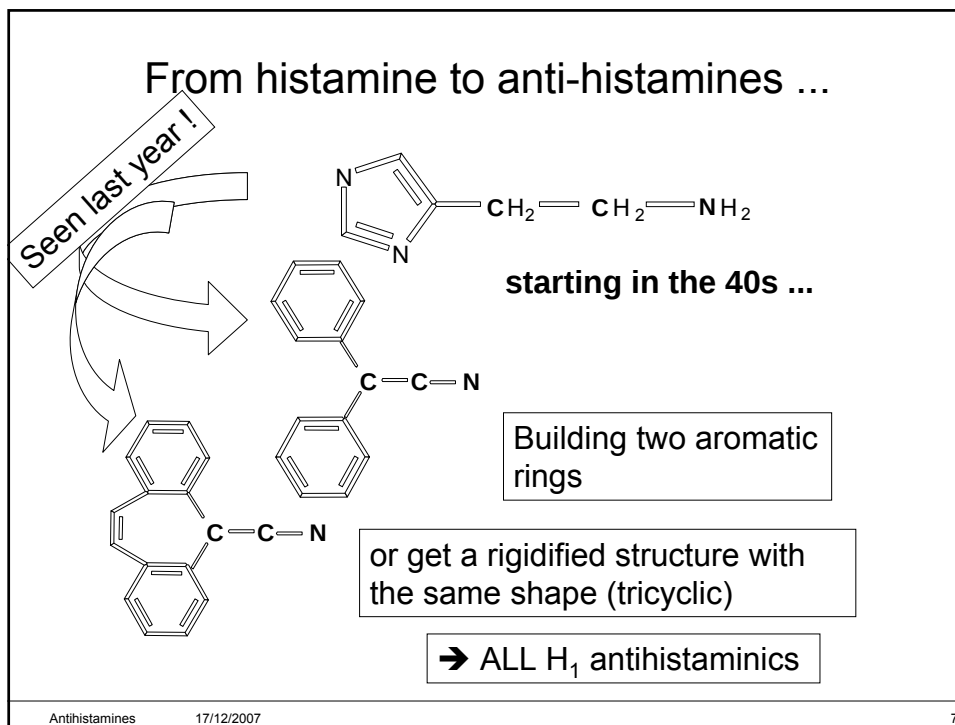
- médiée par les IgG et/ou les IgM
- action directe sur une cellule cible
- implique le complément
- lyse, phagocytose (anémie hémolytique, agranulocytose, thrombopénie)
- délai: 5-12h

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 $TNF\alpha$
- induit typiquement des manifestations cutanées (dermatite de contact, exanthèmes, eczéma, ...)
- délai: 24 à 48h



Rationalization through a deep understanding of the receptor

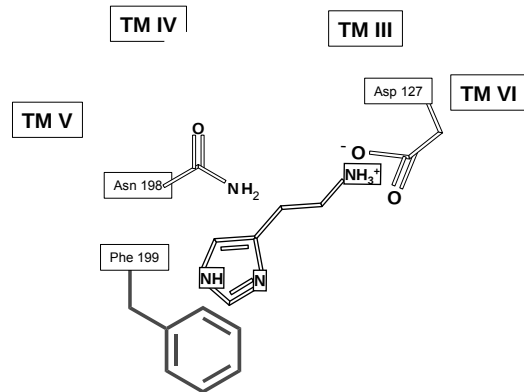
- H₁ receptor
 - CNS
 - périphery

action mediated by the phosphoinositides
- H₂ receptor
 - stomach
 - lung
 - CNS

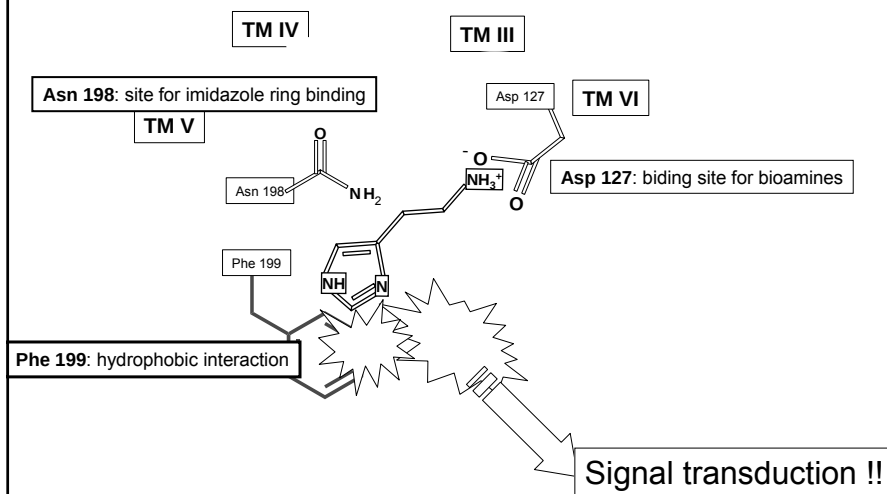
action mediated by cyclic AMP
- H₃ receptor
 - CNS

Antihistamines
17/12/2007
8

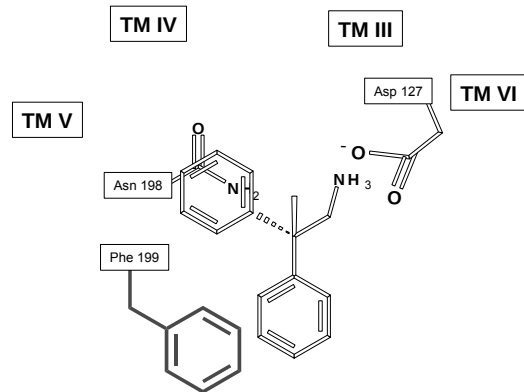
Binding of histamine to H1 receptor



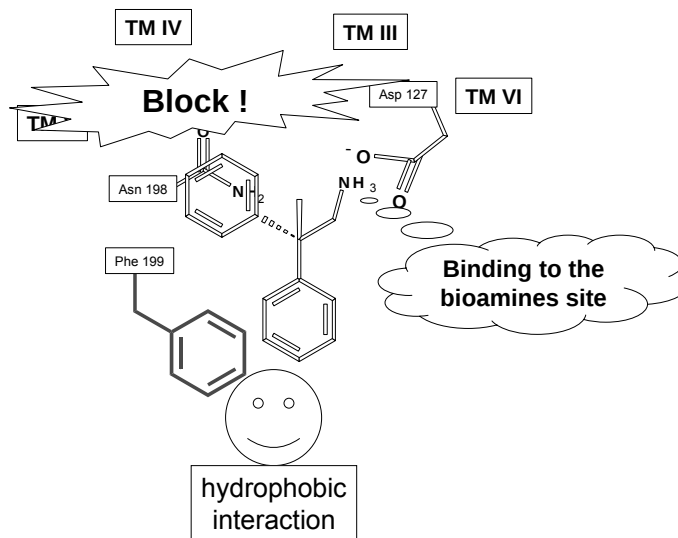
Binding of histamine to H1 receptor



Binding of an antagonist ...



Binding of an antagonist ...



Une famille d'antagonistes H1....

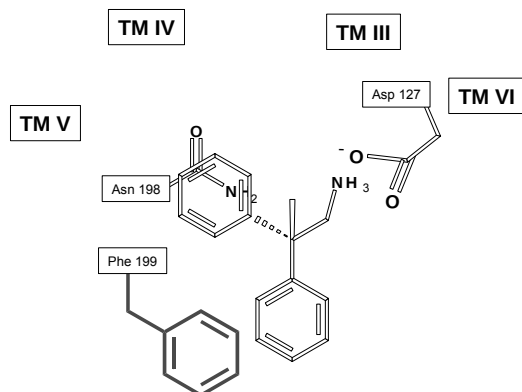
Nom DCI	nom commercial en Belgique *
• alimémazine	THERALENE
• prométhazine	PHENERGAN
• dimenhhydrinate	PARANAUSINE / VAGOMIN
• diphenhydramine	BENYLIN
• dexchlorphéniramine	POLARAMINE
• ciproheptadine	PERIACTIN
• dimétindène	FENISTIL
• méclozine	AGYRAX / POSTAFENE
• cetirizine	ZYRTEC / REACTINE /
• loratadine	CLARITINE / SANELOR
• fexofenadine	TELFAST

et plus récemment

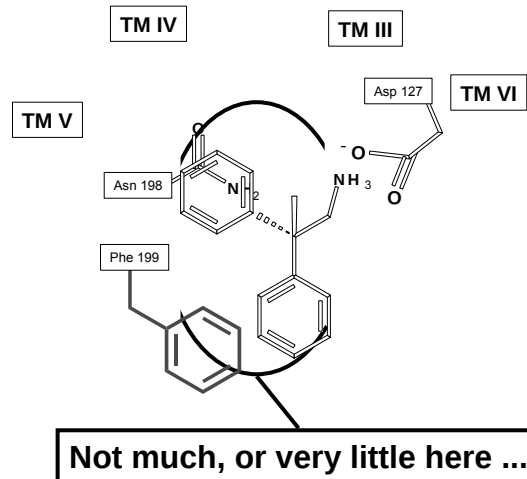
• lévocetirizine	XYZAL
• desloratadine	AERIUS

* liste non limitative...

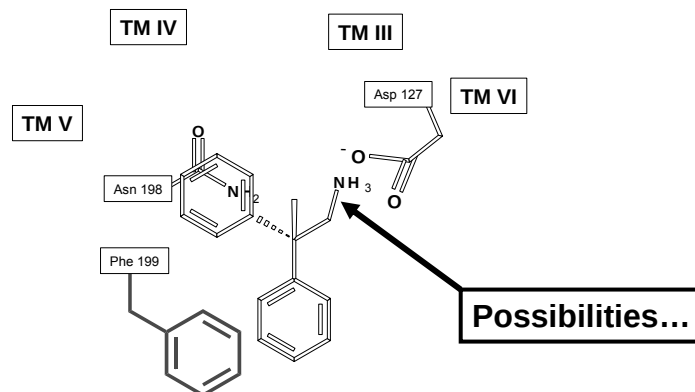
Binding of an antagonist: what can you modify ?



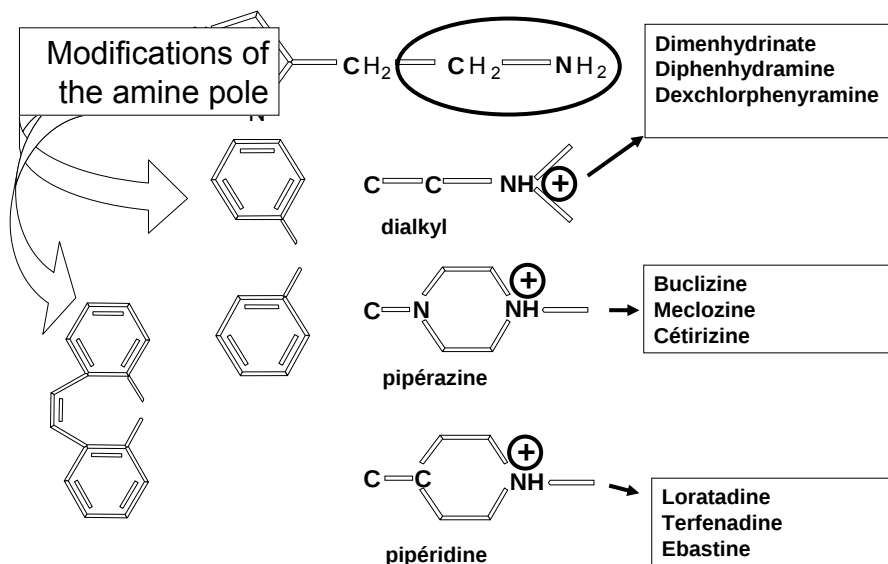
Binding of an antagonist: what can you modify ?



Binding of an antagonist: what can you modify ?



Variations among antihistamines....



Antihistamines

17/12/2007

17

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...

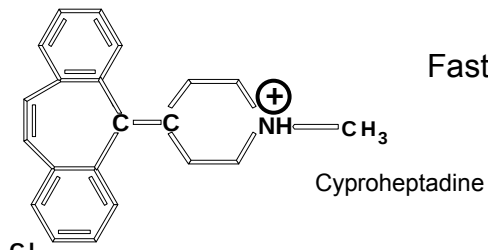
Antihistamines

17/12/2007

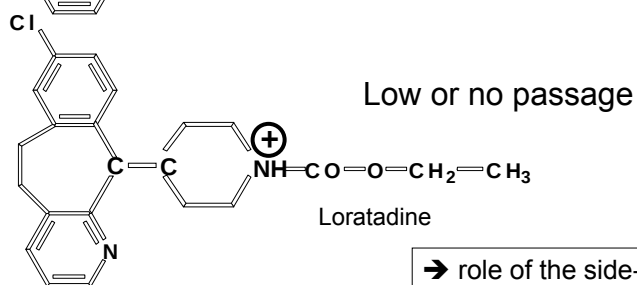
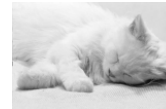
18

Low sedation activity ...

➔ Modulation of the hematoencephalic barrier passage...



Fast and important passage



Low or no passage



➔ role of the side-chain...

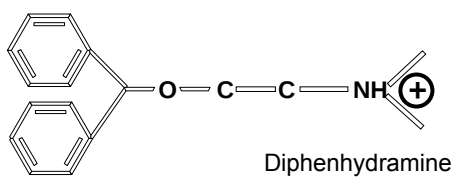
Antihistamines

17/12/2007

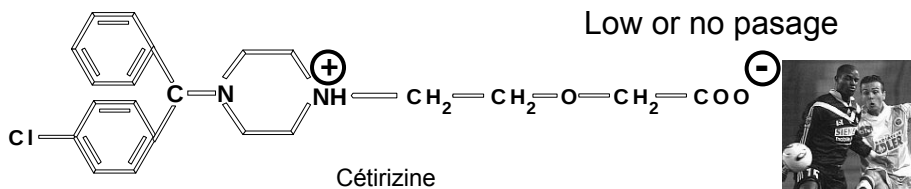
19

Low sedation activity ...

Another example...



Important passage



Low or no passage



➔ role of the length and of the polarity of the side-chain

Antihistamines

17/12/2007

20

Molécules à passage hémato-méningé important et causant de la sédation ...

Nom DCI	sédation	OTC
alimémazine	+++	oui (partiel.)
prométhazine	+++	oui
dimenhydrinate	+++	oui
diphenhydramine	+++	oui
oxomémazine	++	non
dexchlorphéniramine	++	oui
ciproheptadine	++	oui
dimétindène	+	oui
méclozine	+	oui
	+	oui

Antihistamines

17/12/2007

21

The antihistaminic and the sedative actions of the "old" antihistaminics go side by side

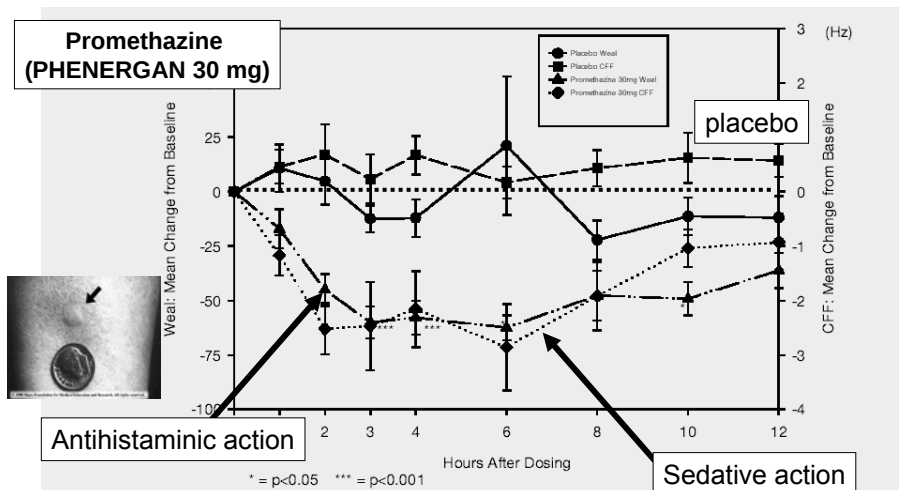


Figure 3. Change from baseline: peripheral antihistaminic suppression (weal) with respect to CFF threshold: acute dose promethazine 30 mg, day 1

Hindmarch et al., Curr. Med. Res. Opin., 17:241-255, 2001

Antihistamines

17/12/2007

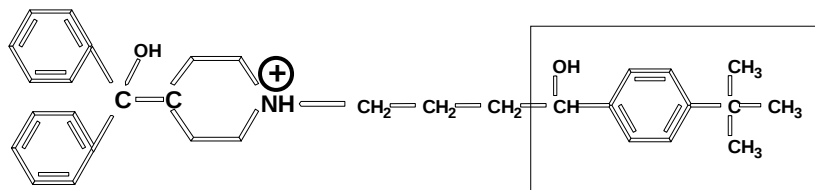
22

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

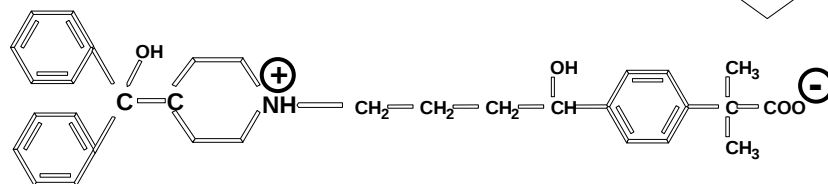
- astémisole
 - terfénadine
- withdrawn because of cardiac toxicity
Torsades de pointe !!!
- fexofénadine
- Active metabolite of terfenadine

The problem of terfanadine...

- terfenadine was a pro-drug

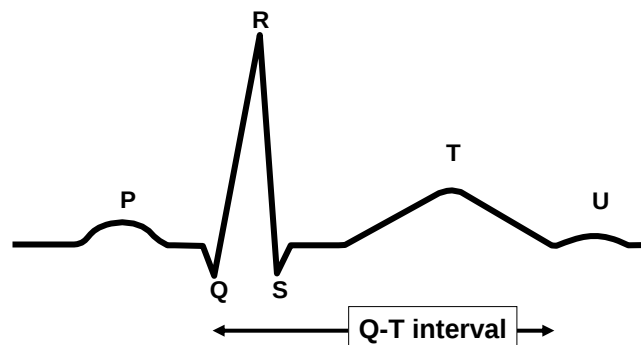


- which underwent a "first pass" liver metabolism that released fexofenadine, the active product

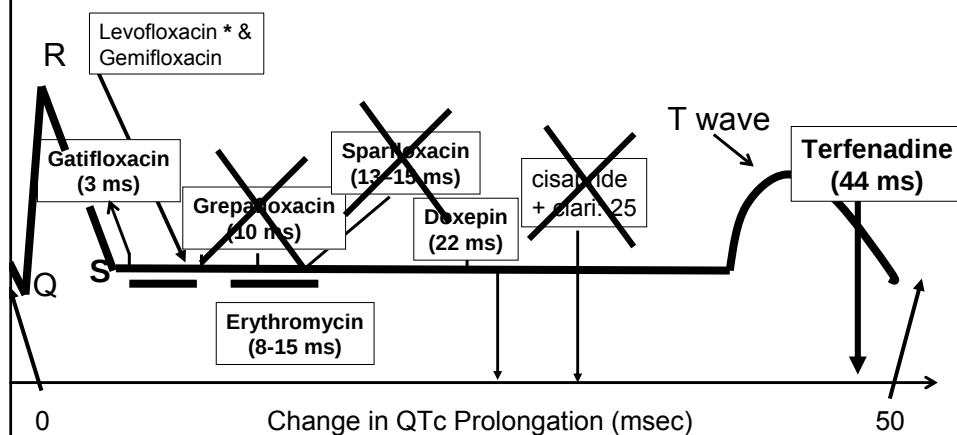


Le problème de la terfénadine ...

- si la terfénadine circule, elle provoque un allongement de l'intervalle Q-T de l'électrocardiogramme pouvant mener à des arythmies mortelles ...



Le problème de la terfénadine ...

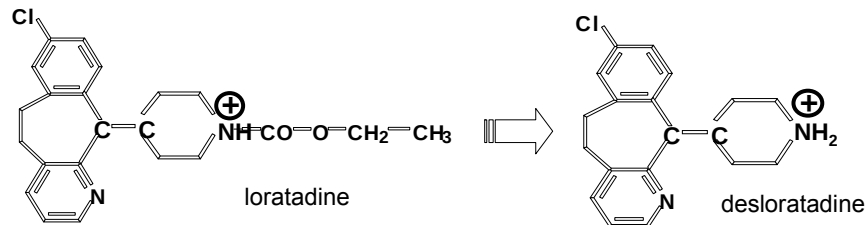


Adapted from Oberg and Bauman, 1995; Baker et al, 1997; van Haarst et al, 1998.

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 antihistaminic and the sedative activities

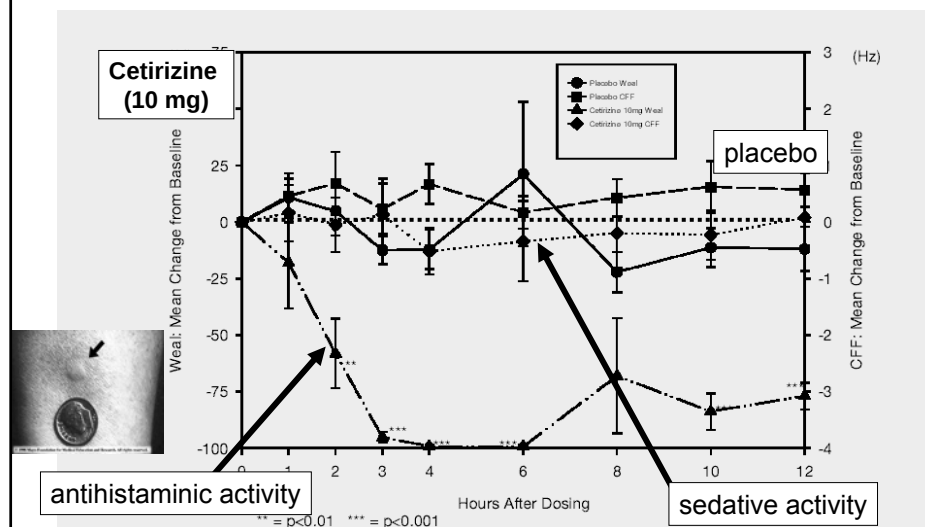


Figure 5. Change from baseline: peripheral antihistaminic suppression (weal) with respect to CFF threshold: acute dose cetirizine 10mg, day 1

Hindmarch et al., Curr. Med. Res. Opin., 17:241-255, 2001

Dissociation des activités antihistaminique et sédatrice ...

Mais, attention:



tout est une question de dose...

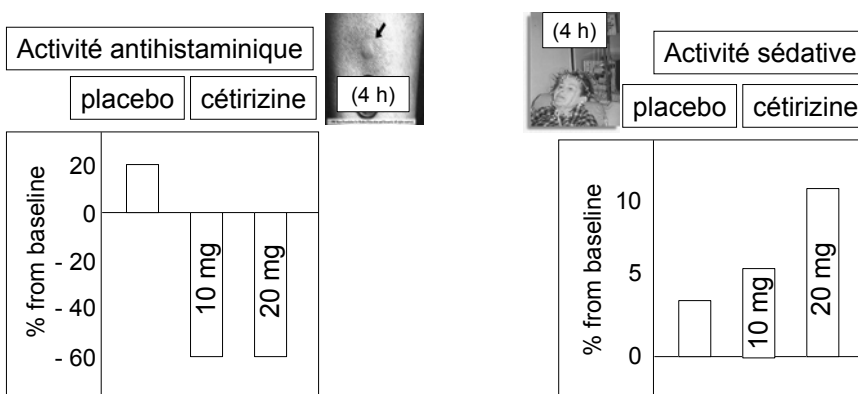
Antihistamines

17/12/2007

29

Dissociation des activités antihistaminique et sédatrice ...

Mais, attention,
tout est une question de dose...



Adapté de Sannita et al., Eur. J. Pharmacol. 300: 33-42, 1996

Antihistamines

17/12/2007

30

L' antihistaminique H1 idéal dans le traitement de l'allergie....

Cahier de charges

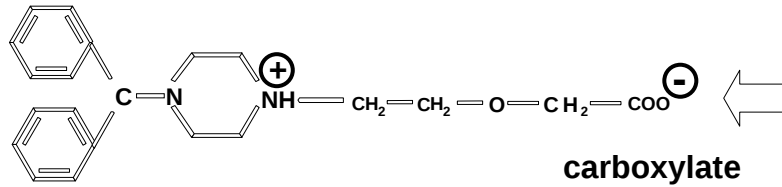
- Pouvoir de sédation faible
- **Eviter les effets anticholinergiques**
 - élevé à moyen pour les anciennes molécules
 - ➔ troubles de la vue, rétention urinaire ...
 - faible à nul pour les nouvelles molécules (loratadine, fexofénadine, cétirizine)
- Obtenir une action rapide et prolongée

L' antihistaminique H1 idéal dans le traitement de l'allergie....

Cahier de charges

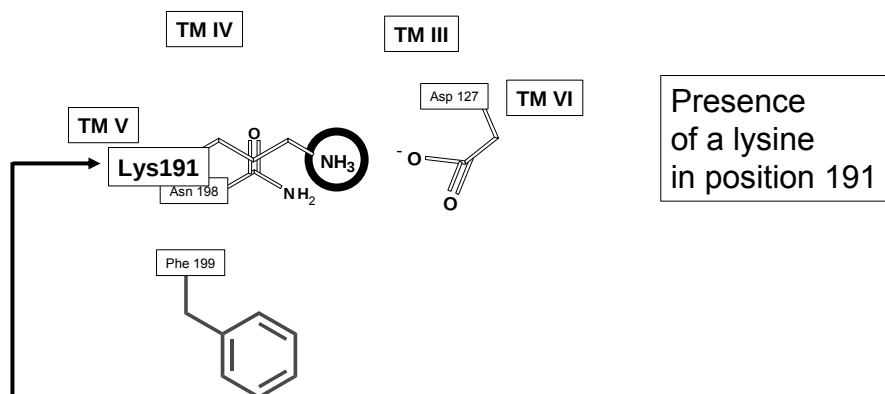
- Pouvoir de sédation faible
- Eviter les effets anticholinergiques
- **Obtenir une action rapide et prolongée**

Propriétés moléculaires de la cétirizine



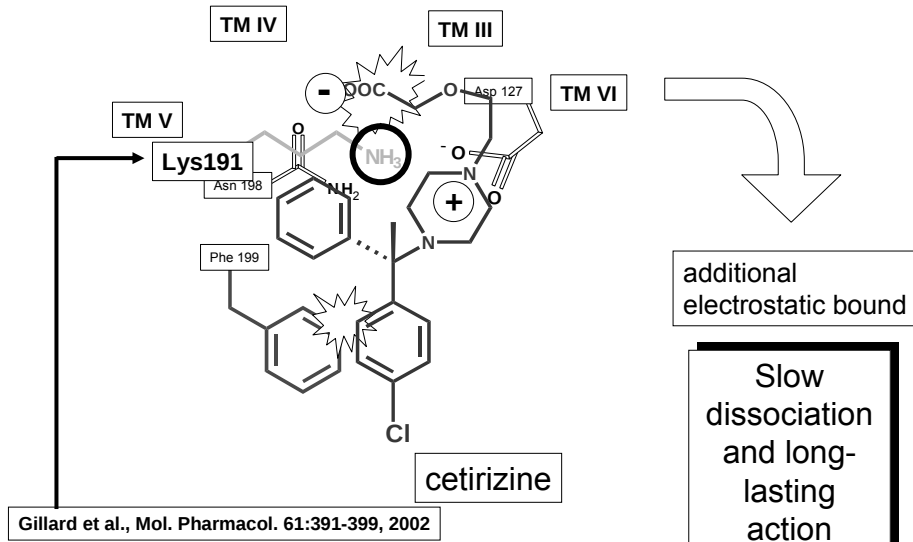
- action directe car pas de nécessité de métabolisme activateur (>< terféndine, loratadine...)
- pas ou peu de passage de la barrière hémato méningée
- **longue durée d'occupation du récepteur**

Binding of an H₁ antagonist to the receptor...



Gillard et al., Mol. Pharmacol. 61:391-399, 2002

Slow release of an antagonist ...



Antihistamines

17/12/2007

35

Prolonged action ...

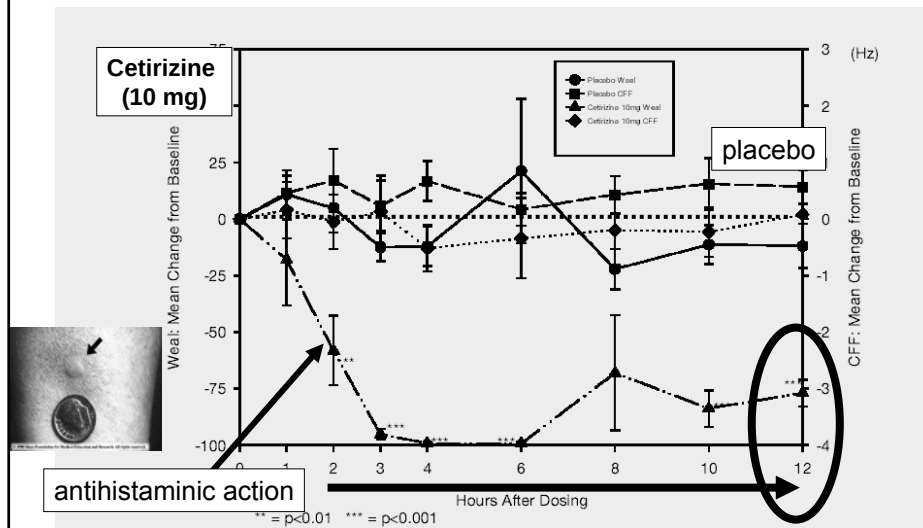


Figure 5. Change from baseline: peripheral antihistaminic suppression (weal) with respect to CFF threshold: acute dose cetirizine 10mg, day 1

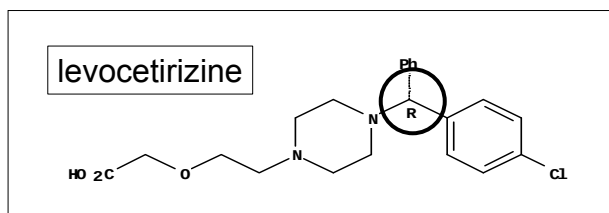
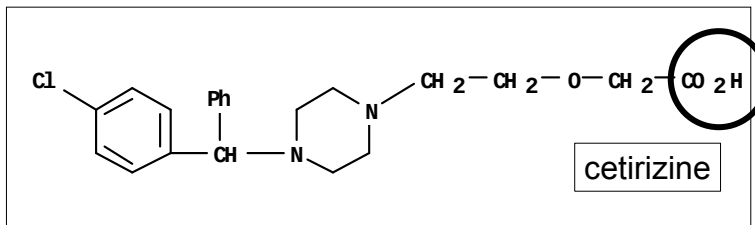
Hindmarch et al., Curr. Med. Res. Opin., 17:241-255, 2001

Antihistamines

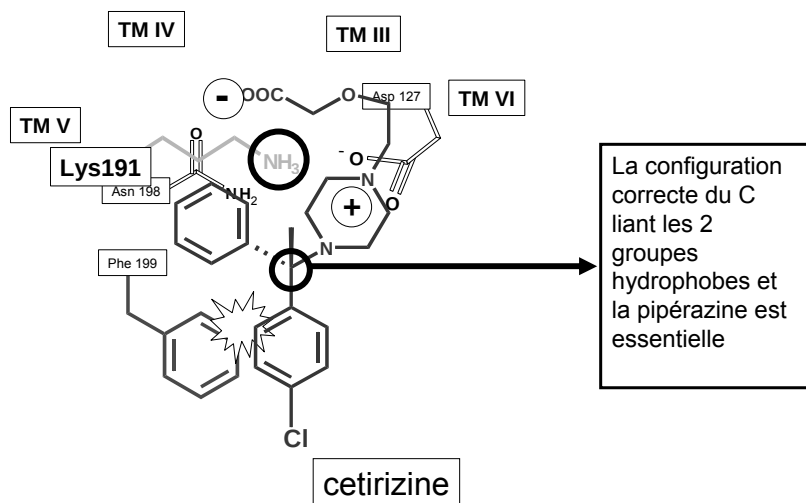
17/12/2007

36

Cetirizine and levocetirizine....



Optic isomers and binding to the receptor ...



Do you speak English in Braine l'Alleud or Gosselies ?

0026-895X/02/6102-391-399\$3.00
MOLECULAR PHARMACOLOGY
Copyright © 2002 The American Society for Pharmacology and Experimental Therapeutics
Mol Pharmacol 61:391-399, 2002

Vol. 61, No. 2
1317/961623
Printed in U.S.A.

Binding Characteristics of Cetirizine and Levocetirizine to Human H₁ Histamine Receptors: Contribution of Lys¹⁹¹ and Thr¹⁹⁴

MICHEL GILLARD, CHRISTY VAN DER PERREN, NICOLE MOGUILEVSKY, ROY MASSINGHAM, and
PIERRE CHATELAIN

UCB S.A. Pharma Sector, In Vitro Pharmacology, Braine l'Alleud, Belgium (M.G., C.V.D.P., R.M., P.C.); and Laboratory of Applied Genetics,
Institute of Molecular Biology and Medicine, Free University of Brussels, Gosselies, Belgium (N.M.)

Received August 28, 2001; accepted November 13, 2001

This paper is available online at <http://molpharm.aspetjournals.org>

Une longue histoire, mais ...

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

Et pour la suite ...

Sur quel point, selon vous, le pharmacien doit-il être particulièrement bien informé par la firme XXX à propos de YYY qui est en vente sans prescription ?

- les propriétés de base du produit
- les indications
- la posologie
- les effets indésirables
- les interactions médicamenteuses

Et pour la vraie suite ...

Quelle est la différence entre A et B ... ?

Cétirizine UCB (UCB)
[cétirizine dichlorhydrate]
compr. (séc.)
20 x 10 mg € 7,00
40 x 10 mg € 12,00

Cétirizine-Ratiopharm (Ratiopharm)
[cétirizine dichlorhydrate]
compr. (séc.)
7 x 10 mg
20 x 10 mg

Zyrtec (UCB)
[cétirizine dichlorhydrate]
compr. (séc.)
7 x 10 mg € 5,21
20 x 10 mg € 9,99
40 x 10 mg € 16,25
gélules
20 ml 10 mg/1 ml
(1 ml = 20 gttex)
sol. (oral)
200 ml 5 mg/5 ml

A

B

C

Généraliste, donc sans supplément au ticket modérateur et en catégorie bon marché

Médicament original avec supplément au ticket modérateur, donc pas en catégorie bon marché

Et pourquoi C est-il sous prescription ?

Et voyons les applications ...

