A simple question...

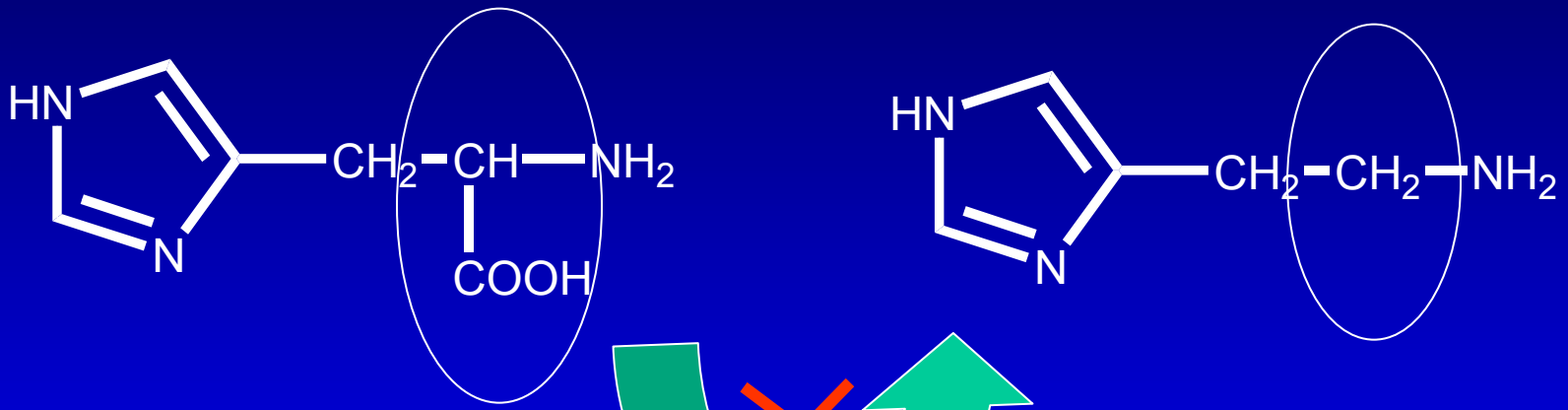
How was histamine discovered ?

- 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 ...



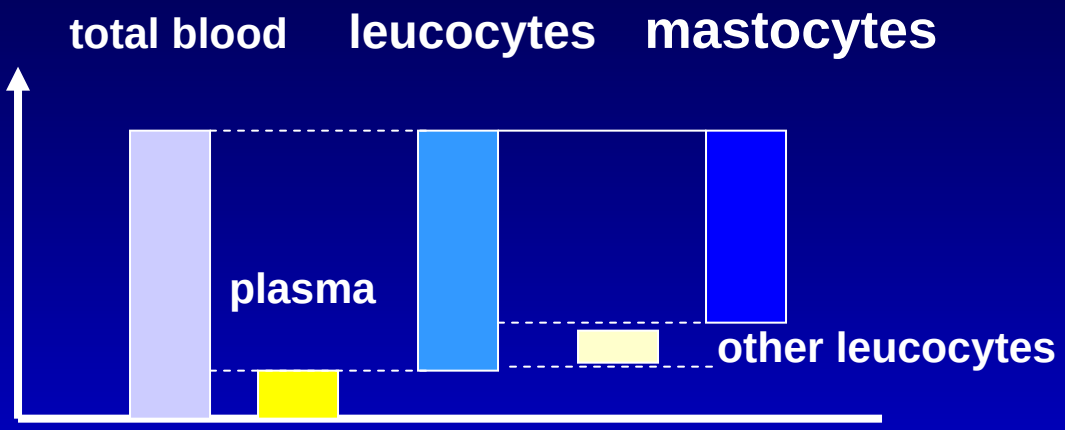
L-histidine decarboxylase

tritoqualine

First inhibitor
of histmine action …
commercialized in France
(HYPOSTAMINE ®)

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 permability and vasodilatation**
  - → rednesses
  - → inflammation
- bronchoconstriction

  important with the guinea-pig but under H_2 retrocontol in man
- **↑ of HCl secretion**

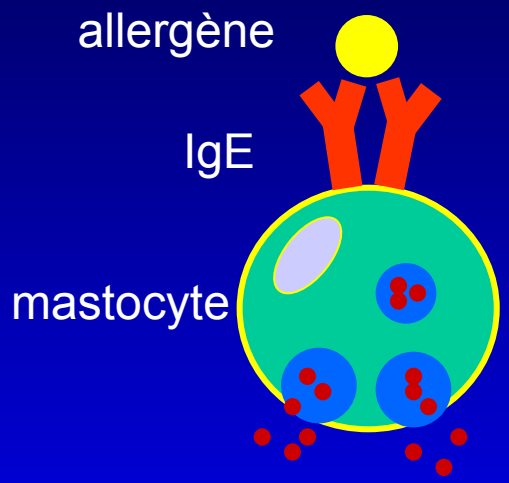
  (pariteal cells of the stomach)
- **neurotransmission**
  - → **awakening reactions, tachycardia, hypertension**
  - → **nauseas, vomitting**
  - → **migraines**

cutaneous signs

neurological and comportmental signs

Rappel: les 4 types de réactions d'hypersensibilité

Réaction de type I anaphylactique



libération d'amines vasoactives dont l'histamine

- 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, phagoytose (anémie hémolytique, agranulocytose, thrombopénie)
- délai: 5-12h

Réaction de type III: formation de complexes immuns

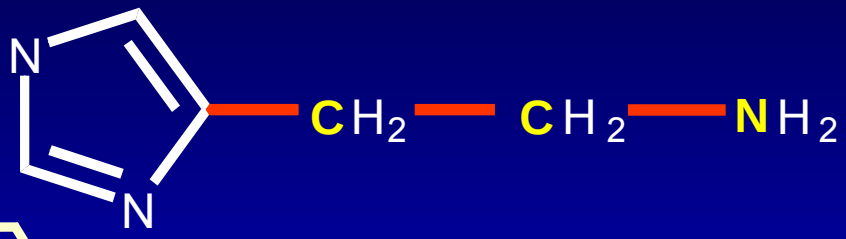
- dépôts dans les tissus avec réaction inflammatoire disséminée
- activation du complément et libération de toxines des leucocytes
- agrégation plaquettaire, microthrombonses…
- délai: 3-8h

Réaction de type IV : cellulaire

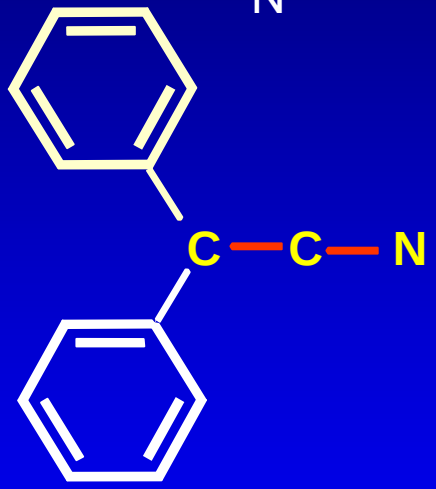
- activation directe des cellules T
- libération de cytokines et de TNFα
- induit typiquement des manifestations cutanées (dermatite de contact, exanthèmes, eczema, …)
- délai: 24 à 48h

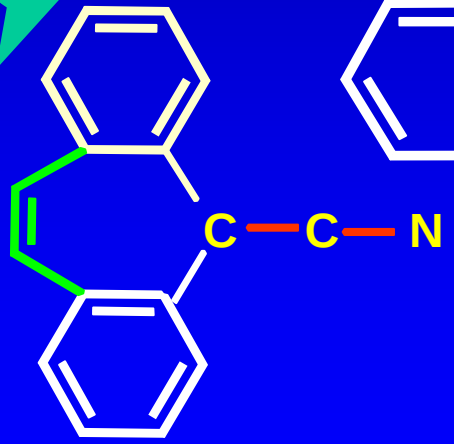
From histamine to anti-histamines ...

Seen last year !



starting in the 40s ...





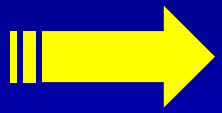
Building two aromatic rings

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

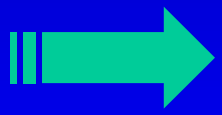
➔ ALL H_1 antihistaminics

Rationalization through a deep understanding of the receptor

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

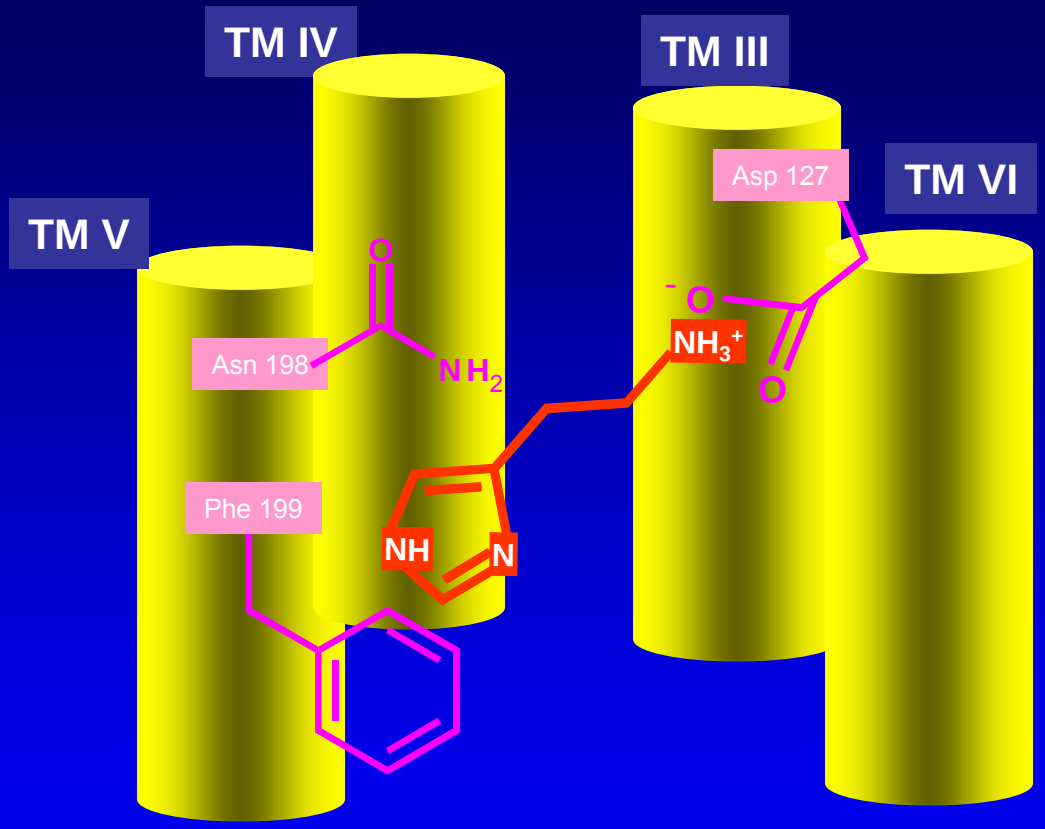


action mediated by the phosphoinositides

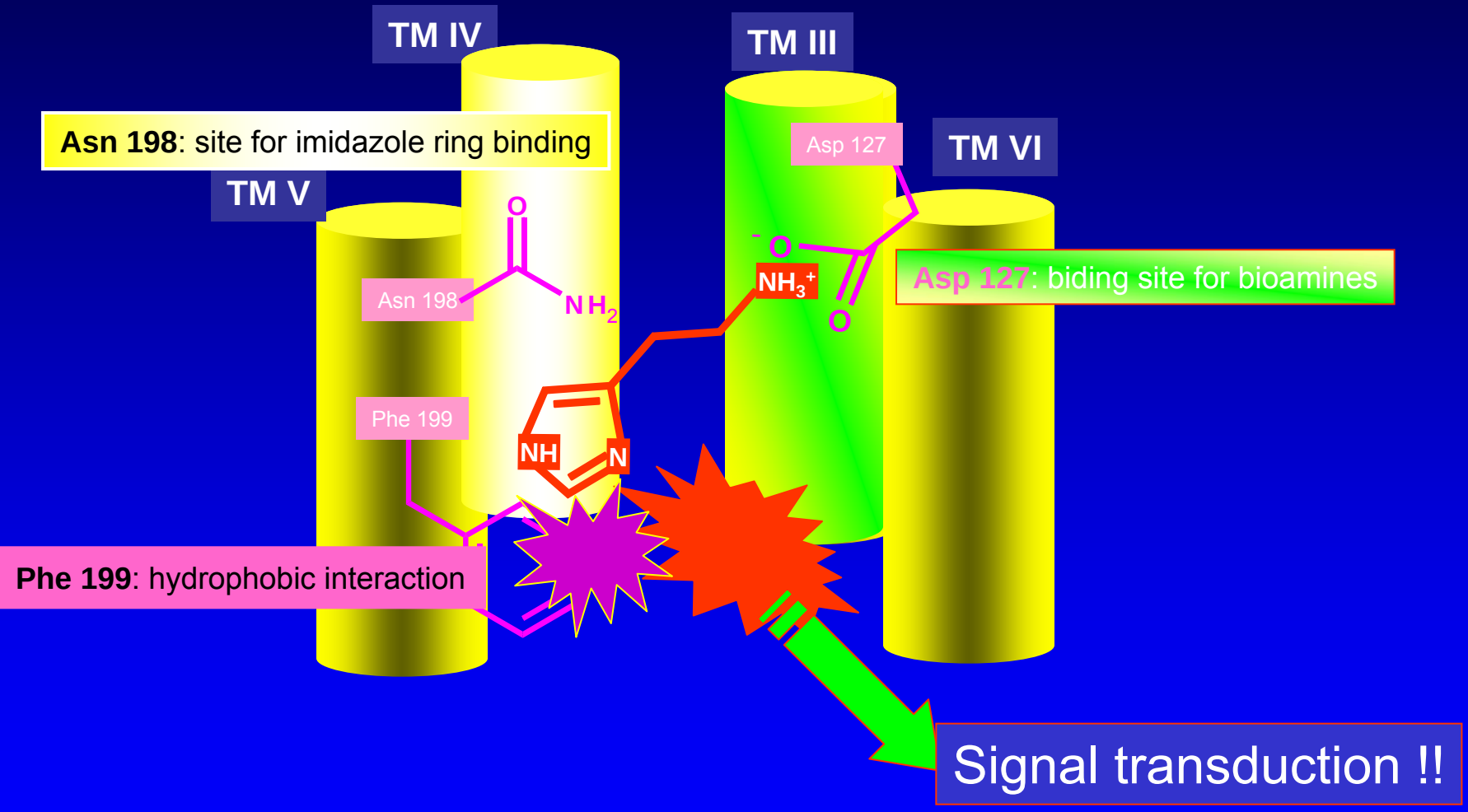


action mediated by cyclic AMP

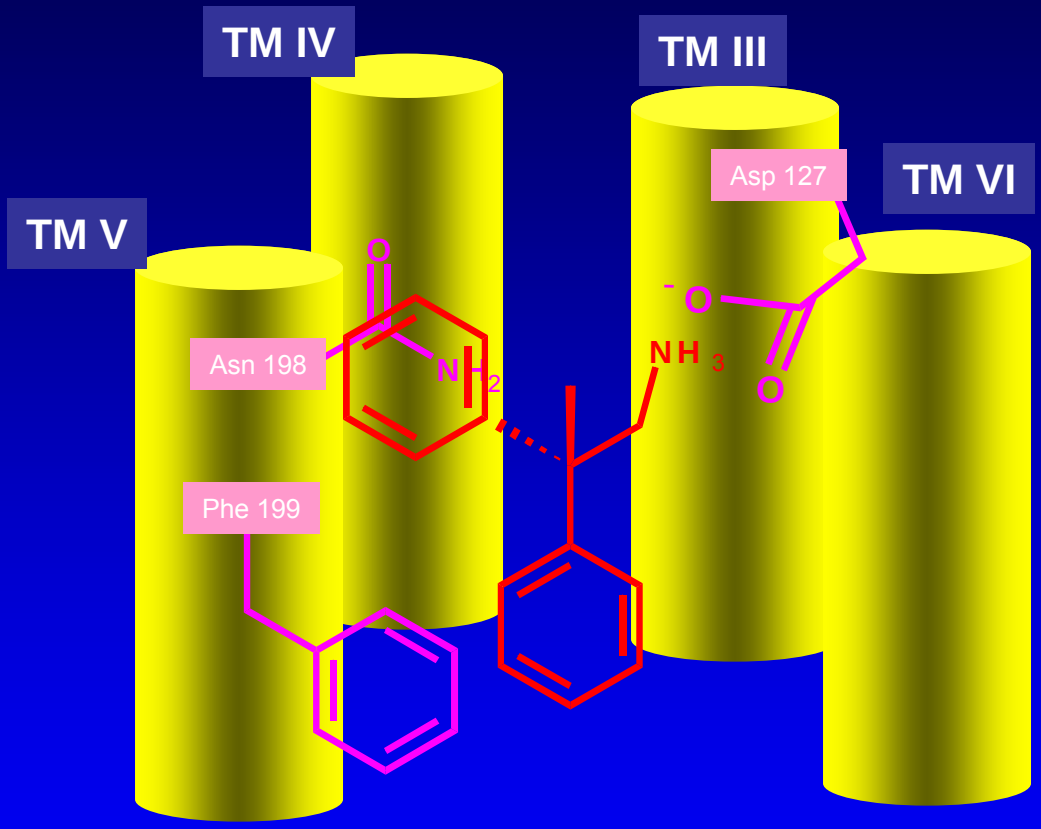
Binding of histamine to H1 receptor



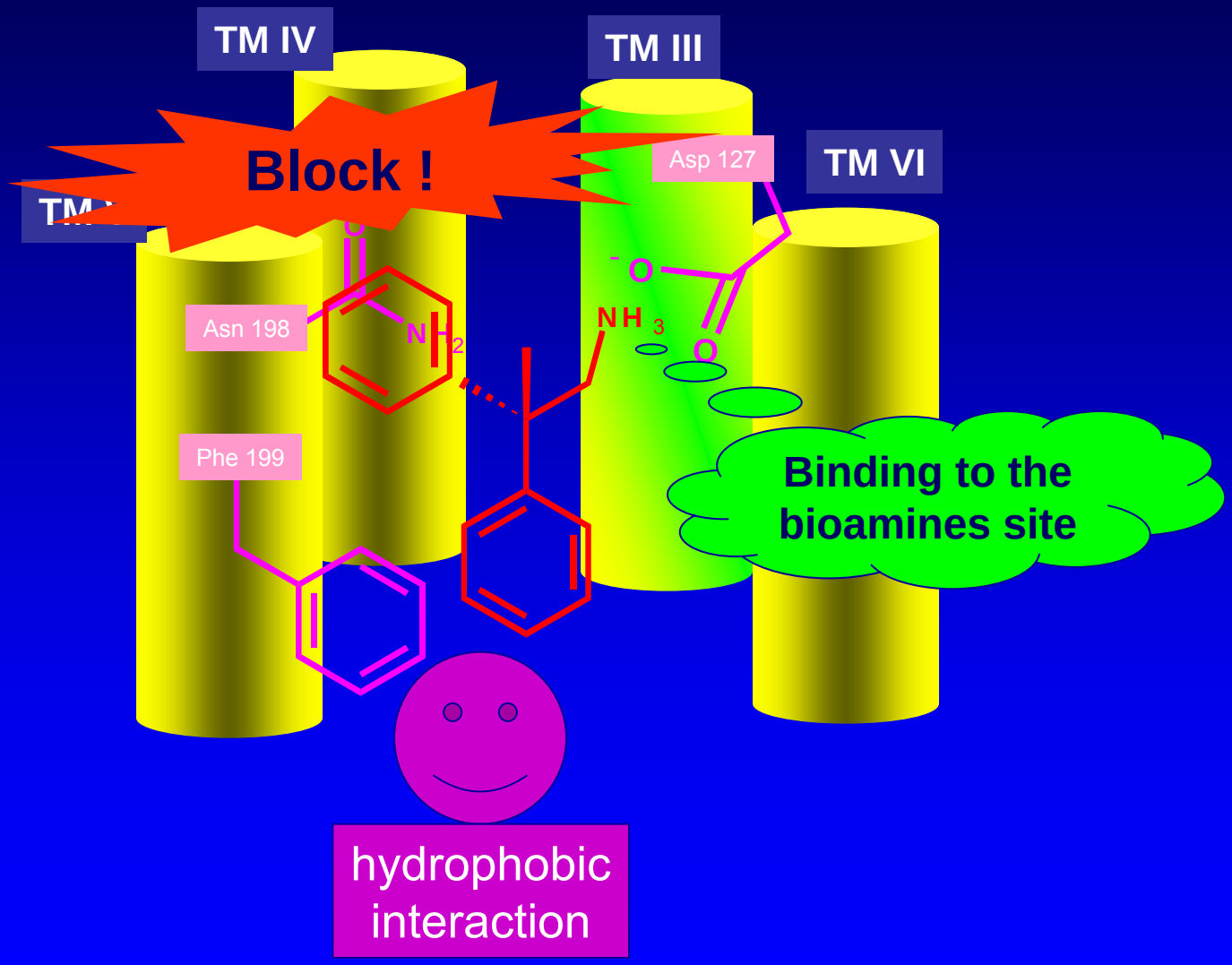
Binding of histamine to H1 receptor



Binding of an antagonist ...



Binding of an antagonist ...



Une famille d'antagonistes H1….

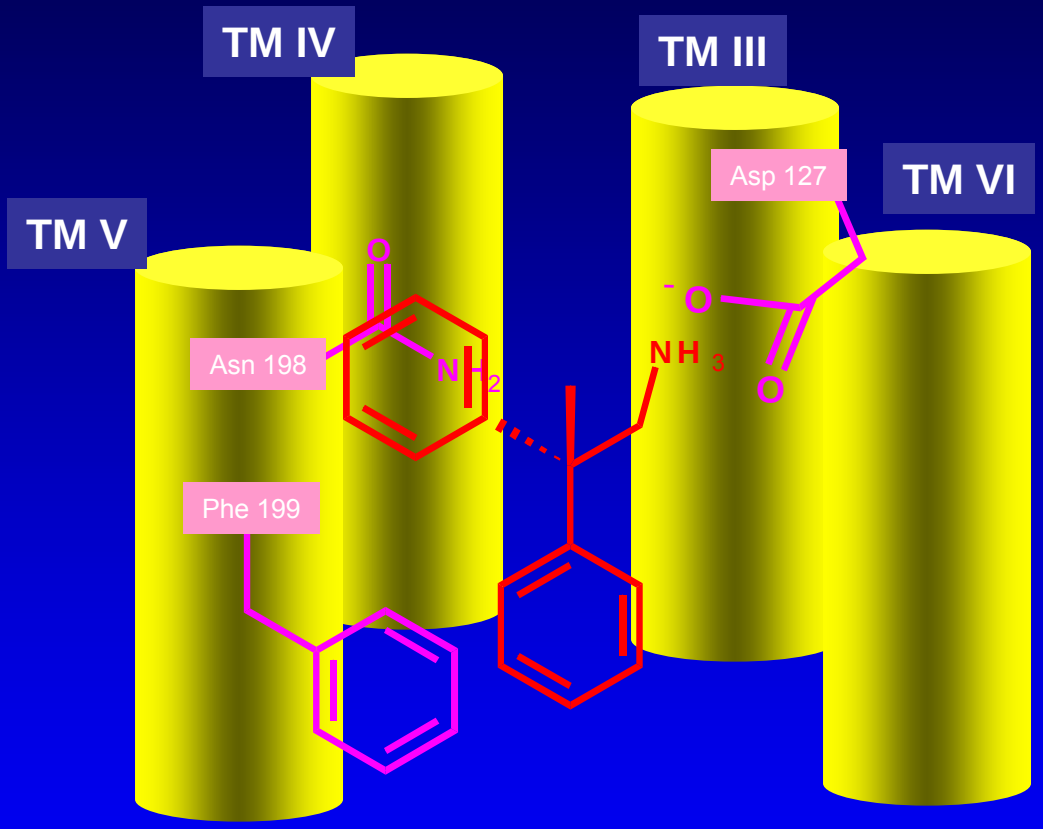
Nom DCI	nom commercial en Belgique *
• alimémazine	THERALENE
• prométhazine	PHENERGAN
• dimenhydrinate	PARANAUSINE / VAGOMIN
• diphenhydramine	BENYLIN
• dexchlrorphéniramine	POLARAMINE
• ciproheptadine	PERIACTIN
• dimétindène	FENISTIL
• méclozine	AGYRAX / POSTAFENE
• cetirizine	ZYRTEC / REACTINE / ….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

et plus récemment

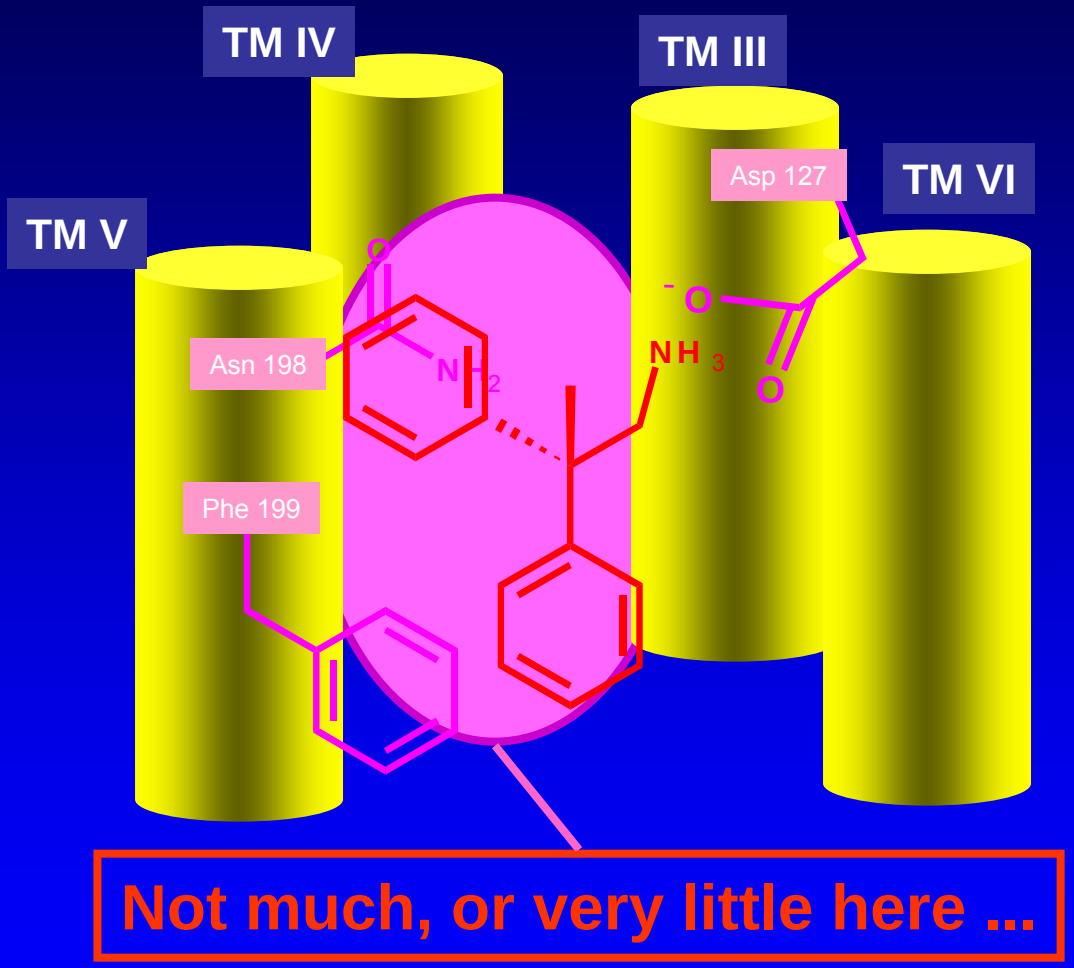
• lévocetirizine	XYZAL
• desloratadine	AERIUS

* liste non limitative…

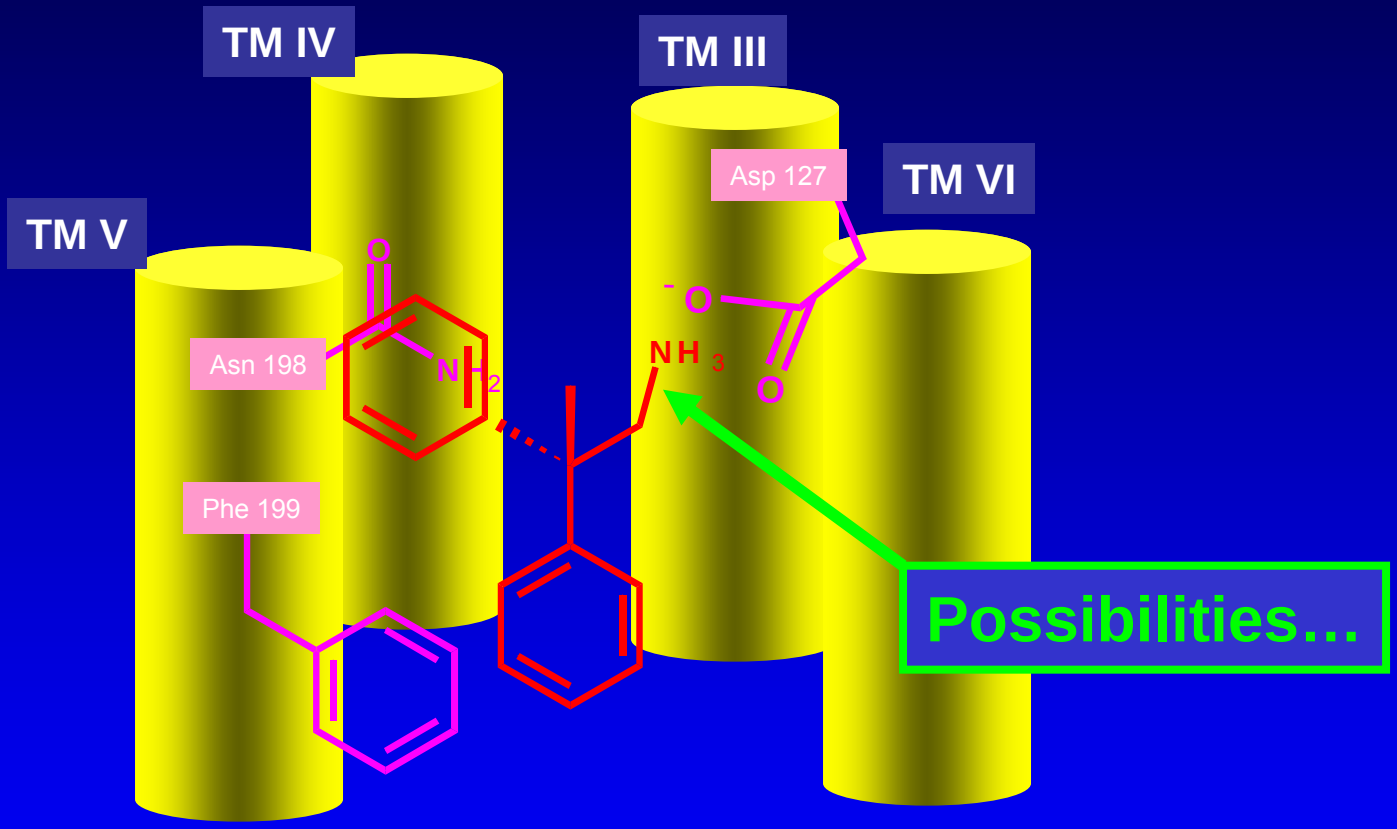
Binding of an antagonist: what can you modify ?



Binding of an antagonist: what can you modify ?

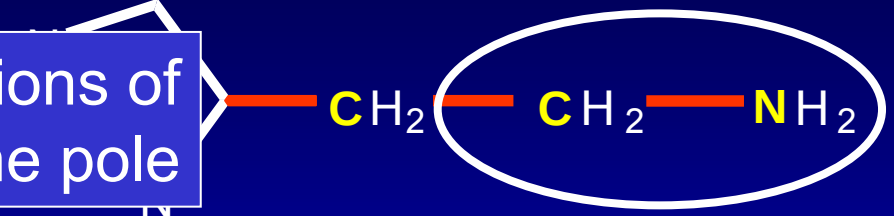


Binding of an antagonist: what can you modify ?

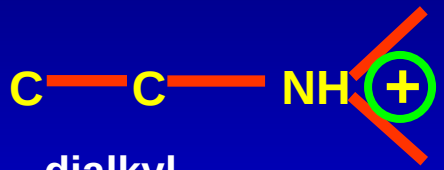


Variations among antihistamines....

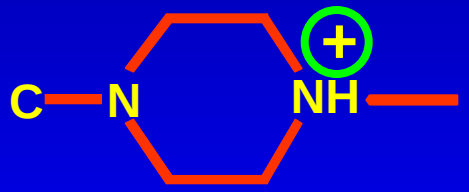
Modifications of the amine pole



Dimenhydrinate
Diphenhydramine
Dexchlorphenyramine

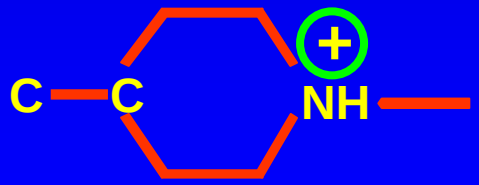


dialkyl



pipérazine

Buclizine
Meclozine
Cétirizine



pipéridine

Loratadine
Terfenadine
Ebastine

The ideal antihistaminic drug for the treatment of allergy

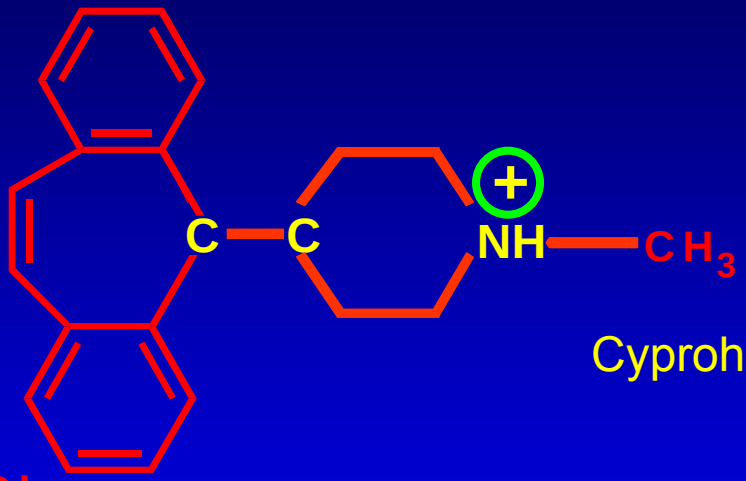
What is your "wish list" ?

- 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…

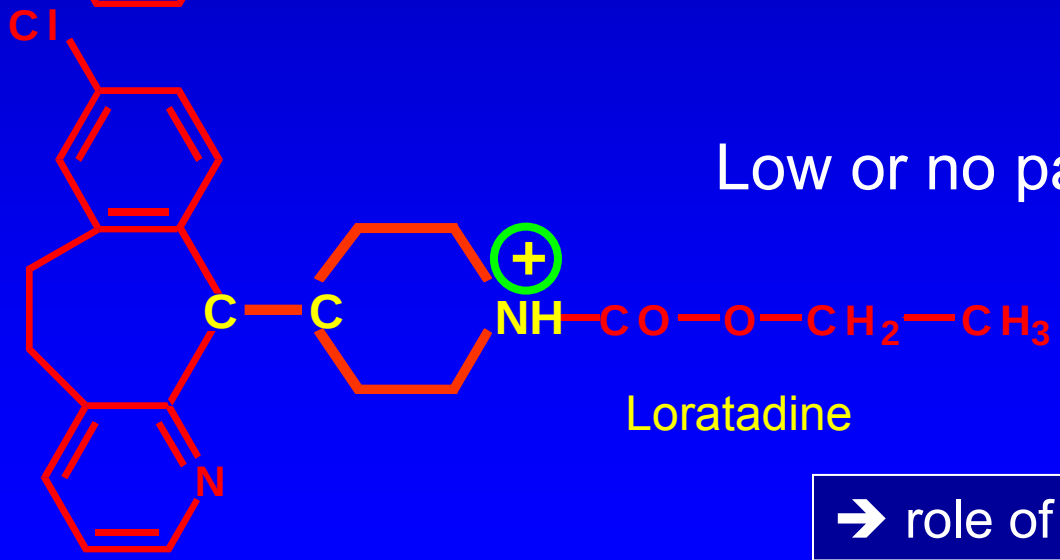
Low sedation activity ...

➔ **Modulation of the hematoencephalic barrier passage...**



Cyproheptadine

Fast and important passage



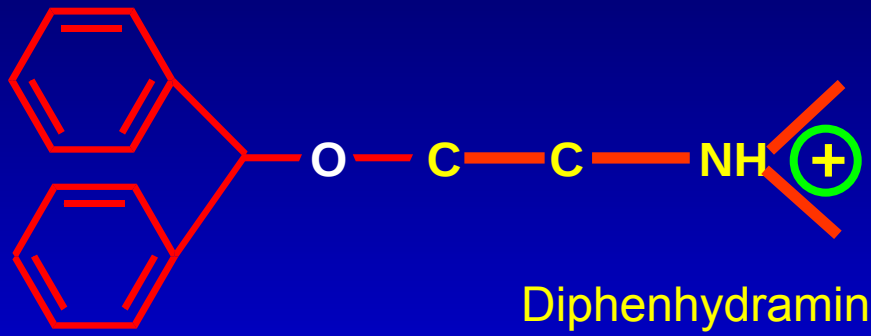
Loratadine

Low or no passage

➔ role of the side-chain...

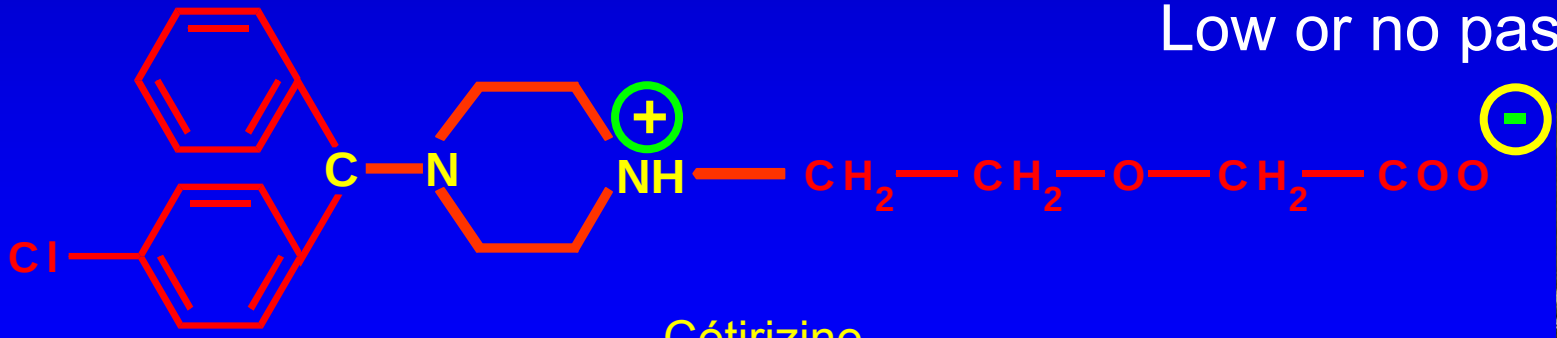
Low sedation activity ...

Another example…



Diphenhydramine

Important passage



Cétirizine

Low or no pasage

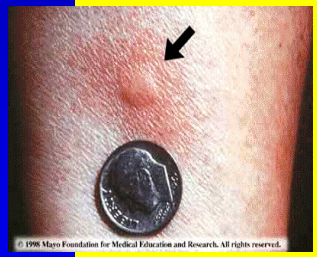
➔ role of the length and of the polarity of the side-chain

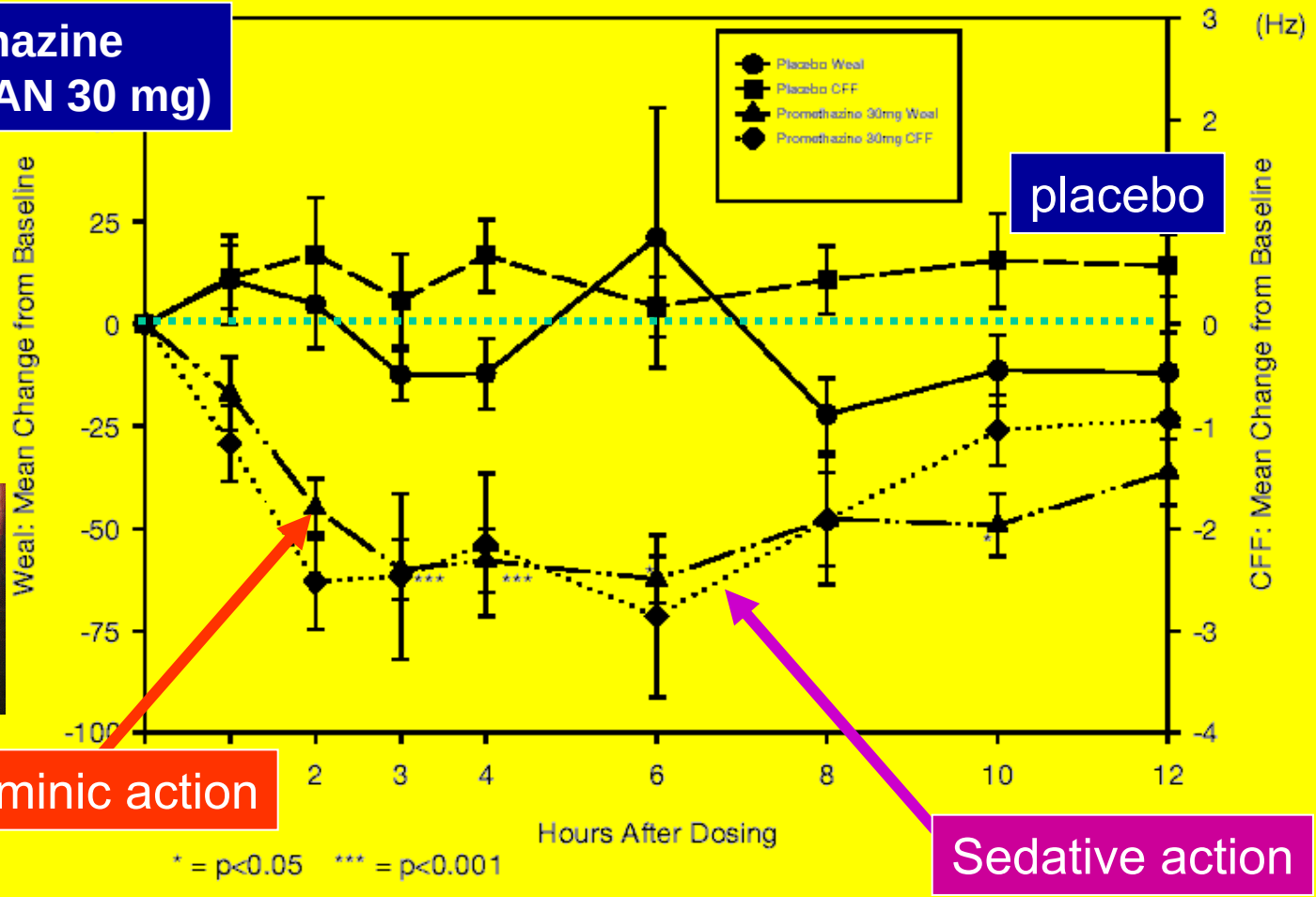
Molécules à passage hémato-méningé important et causant de la sédation ...

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

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

Promethazine (PHENERGAN 30 mg)





placebo

Antihistaminic action

Sedative action

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

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

- astémisole
- terfénadine

withdrawn because of cardiac toxicity
Torsades de pointe !!!

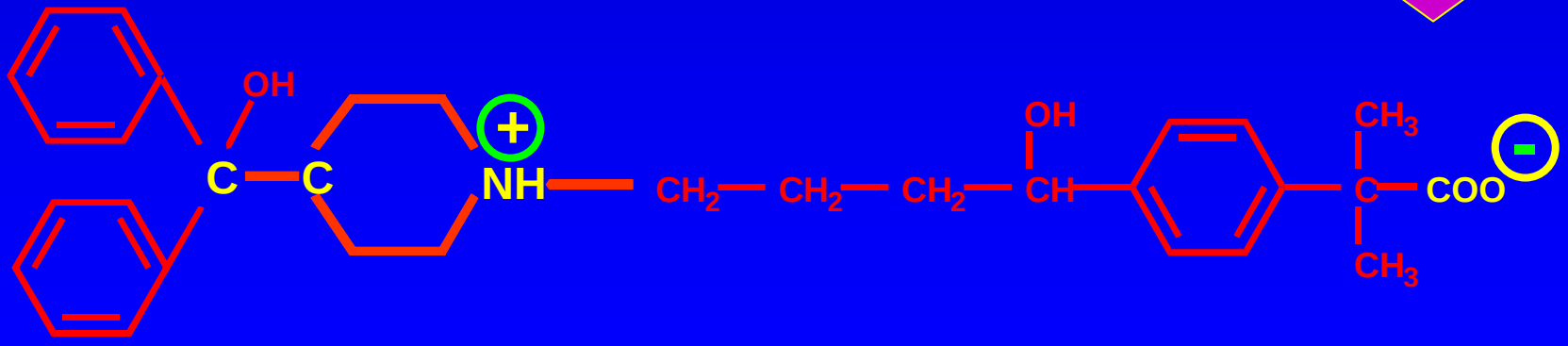
- fexofénadine

Active metabolite of terfenadine

What was terfenadine...

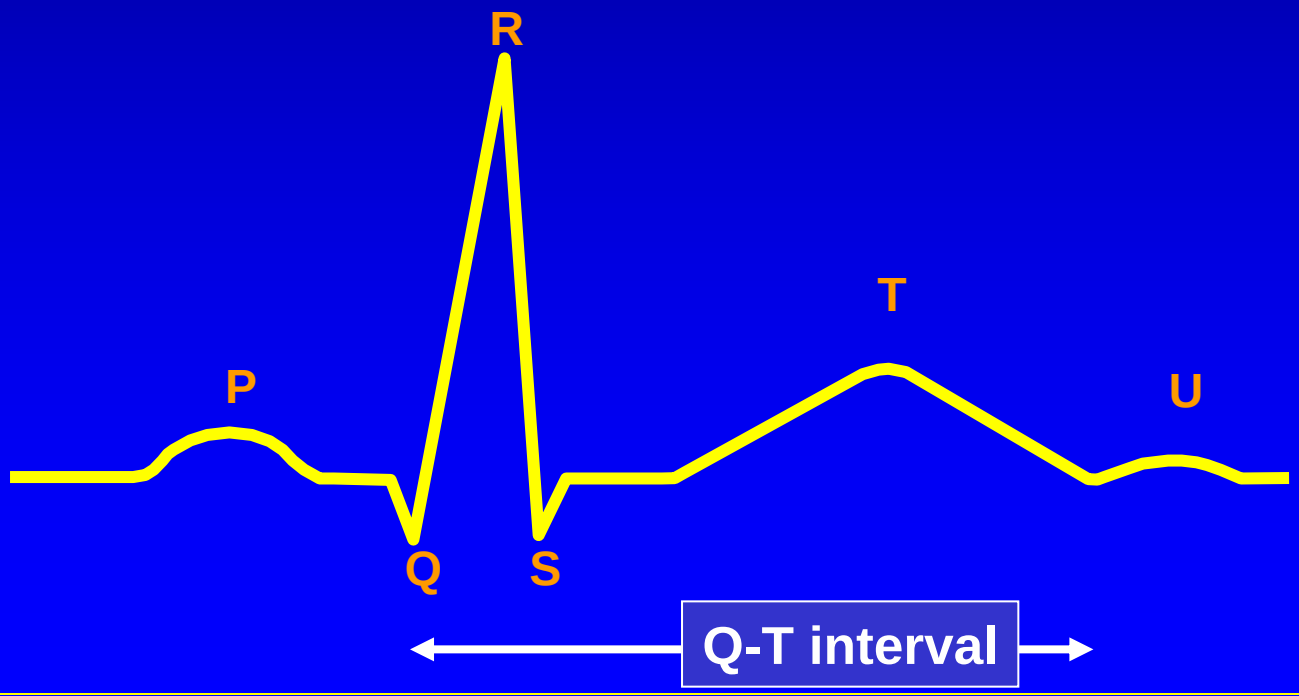
- **terfenadine was a pro-drug**

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

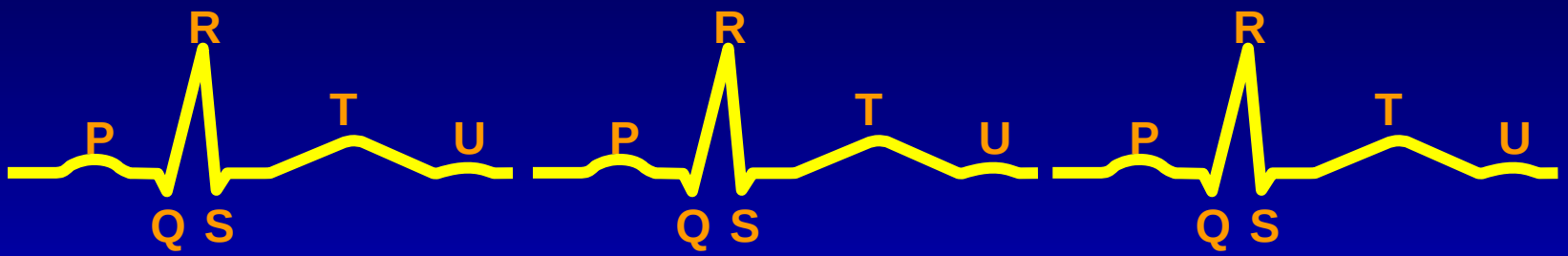


The main problem of terfenadine ...

- 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** arythmia and "***Torsades de pointes***" ...



What is "Torsades de pointe" ?



J. Simkó et al. Proarrhythmic Potential of Antimicrobial Agents

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.

Mechanism(s) of Torsade de Pointe

1. Role of ectopic beats

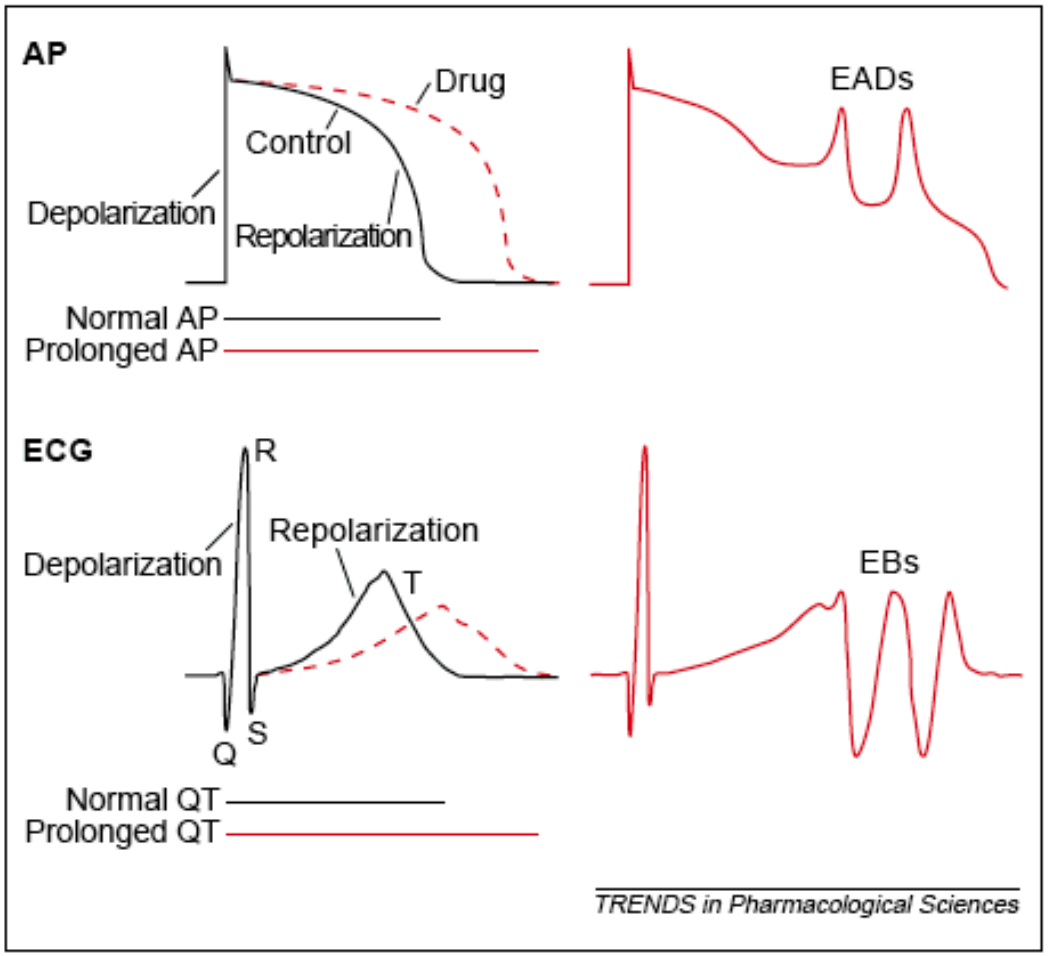


Figure 1. The relationship between ventricular transmembrane action potentials (APs) and the surface electrocardiogram (ECG). In the ECG traces the QRS and T waves denote the depolarization and repolarization, respectively, of the ventricles. The QT interval represents the time elapsed between the ventricular depolarization and repolarization. An increase in the duration of the AP (APD) is responsible for the prolongation of the QT interval. Shown on the left are the APs and ECG in the absence (control) and presence of a drug [e.g. a blocker of the rapid component of the delayed rectifier K^+ current (I_{Kr})] that prolongs the APD and consequently the QT interval. Shown on the right are two large early afterpolarizations (EADs) occurring during the repolarization phase of a prolonged AP, giving rise to two ectopic beats (EBs) in the ECG trace.

Balardinelli *et al*. TIPS (2003) 24:619-625

Mechanism(s) of Torsade de Pointes

2. role of dispersion of ventricular repolarization

Balardinelli *et al*. TIPS (2003) 24:619-625

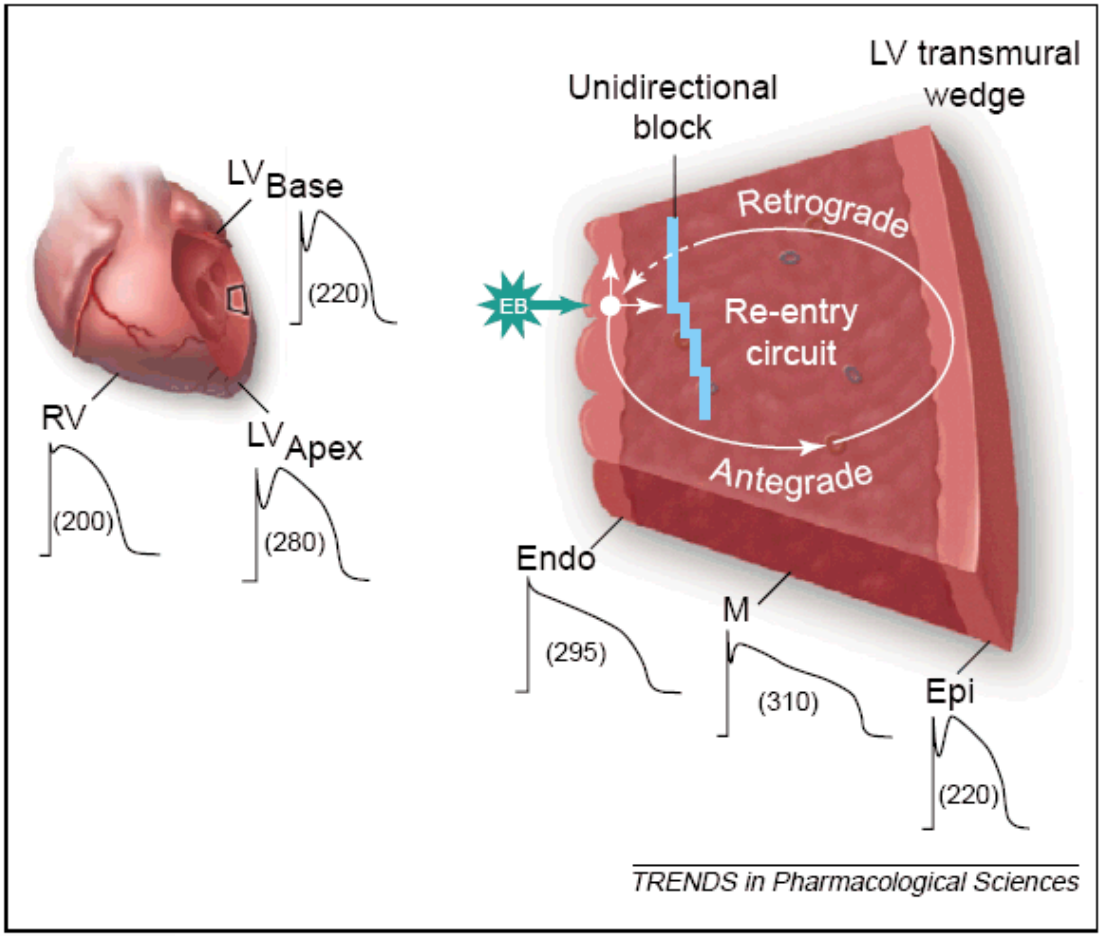


Figure 3. Heterogeneity of ventricular repolarization caused by regional differences in action potential duration and the development of a re-entrant circuit. A heart and a transmural wedge of the left ventricle are shown with action potential (APs) and a re-entrant circuit. The APs shown are representative examples from the right and left (base and apex) ventricles (RV and LV, respectively), and the endocardial (Endo), mid-myocardial (M) and epicardial (Epi) regions across the LV wall. The numbers in parentheses denote the duration (in milliseconds) of the APs. The differences in the durations of the action potentials (APDs) are responsible for the heterogeneity of refractoriness, which in turn create the substrate for re-entrant arrhythmias, such as torsade de pointes. A re-entrant circuit that includes myocardial cells from the endocardial, mid-myocardial and epicardial regions of the LV transmural wedge is shown together with a region of functional unidirectional block (thick blue line) created by the long APDs of the mid-myocardium (long refractory period), and the reentrant excitation wave front (white line with arrows). A simplified sequence of events that can initiate re-entry includes the following. (i) A premature beat [ectopic beat (EB)], presumably brought about by an early afterdepolarization, encounters a region of functional unidirectional block in its propagation path. (ii) The EB, however, propagates laterally through myocardium that is not refractory (cells with shorter APDs), resulting in excitation of the endocardium. (iii) This excitation wave front continues in an antegrade direction to excite various portions of the mid-myocardium, and the epicardium. (iv) The excitation wave front twists around and propagates in the opposite direction towards the endocardium (i.e. retrograde conduction) to activate the remainder of the mid-myocardium. (v) Finally, the wave front crosses the region of unidirectional block no longer refractory (dashed white line with arrow), to re-enter and thereby re-excite the endocardium. For a more detailed description of the electrophysiological basis for re-entry the reader is referred to Ref. [9].

Risk of Torsade de pointes and inhibitors of cyt P450 metabolism

Table 1

QT interval prolonging drugs metabolized by CYP 3A4, which may possibly interact both pharmacokinetically and phamacodinamically with macrolides and imidazole antifungals.

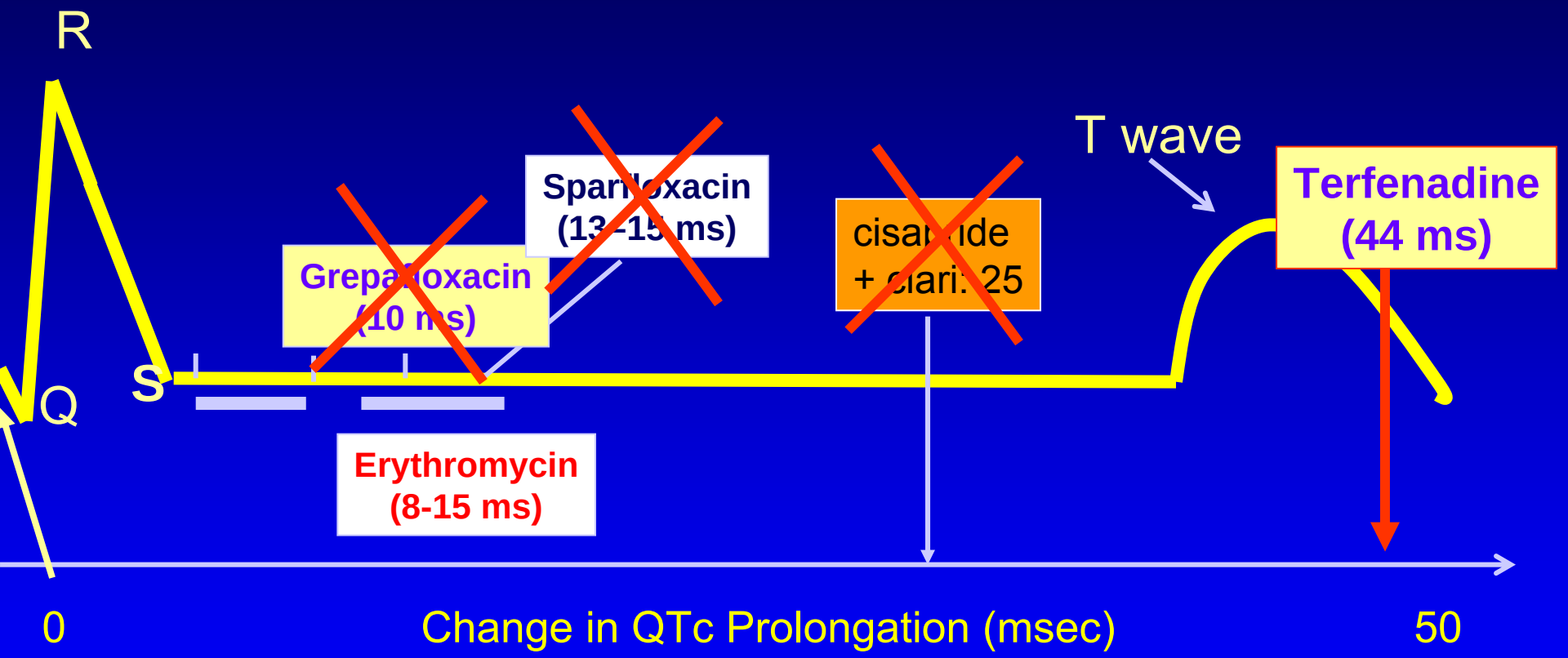
Antiarrhythmics	Amiodarone (with roxithromycin [23]), quinidine (with erythromycin [116]), disopyramide (with clarithromycin [117, 118])
Antifungals	Fluconazole, ketoconazole, itraconazole, miconazole
Prokinetics	Cisapride (with clarithromycin, [119, 120], with erythromycin [121])
Antihistamines	Terfenadine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

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

disponible sur i-campus →

Simkó et al., Infection 2008;36:194-206

Molecules withdrawn because of risk of QT prolongation and *Torsades de pointe*

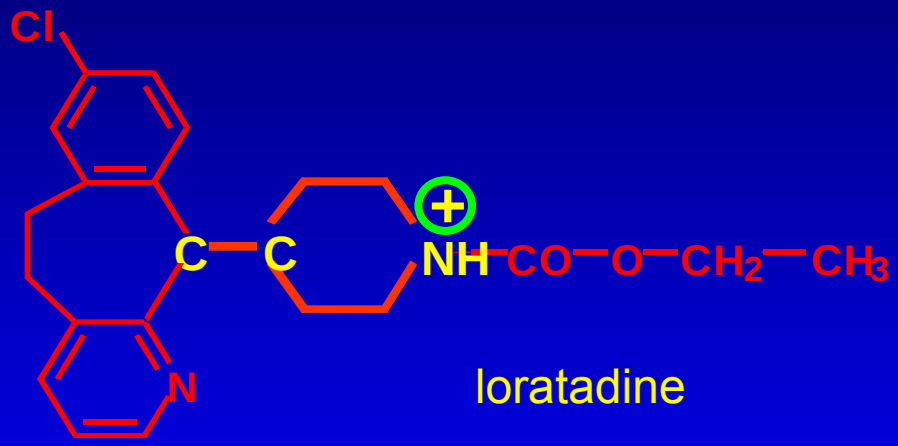


Adapted from Oberg and Bauman,1995; Baker et al,1997; van Haarst et al, 1998.

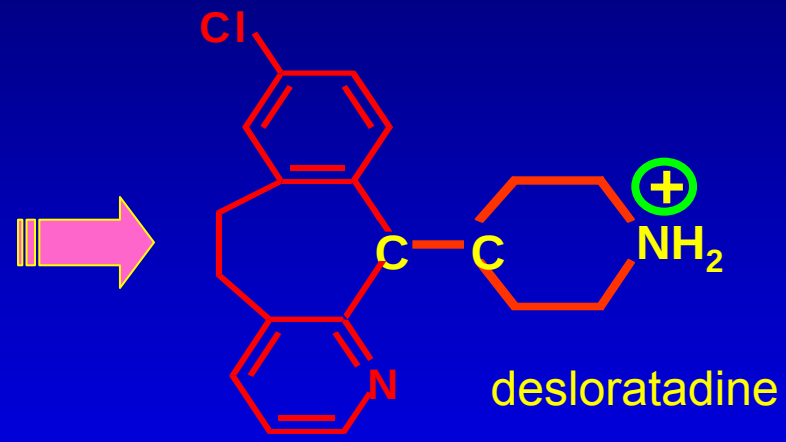
Molecules with a weak hemato-encephalic passage ...

- loratadine

must be metabolized into desloratadine



loratadine

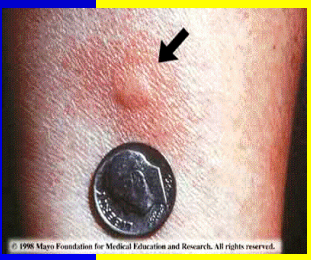


desloratadine

- ebastin
- cetirizine

not very sedative and acting as such

Dissociation of the antiallergic and sedative activities



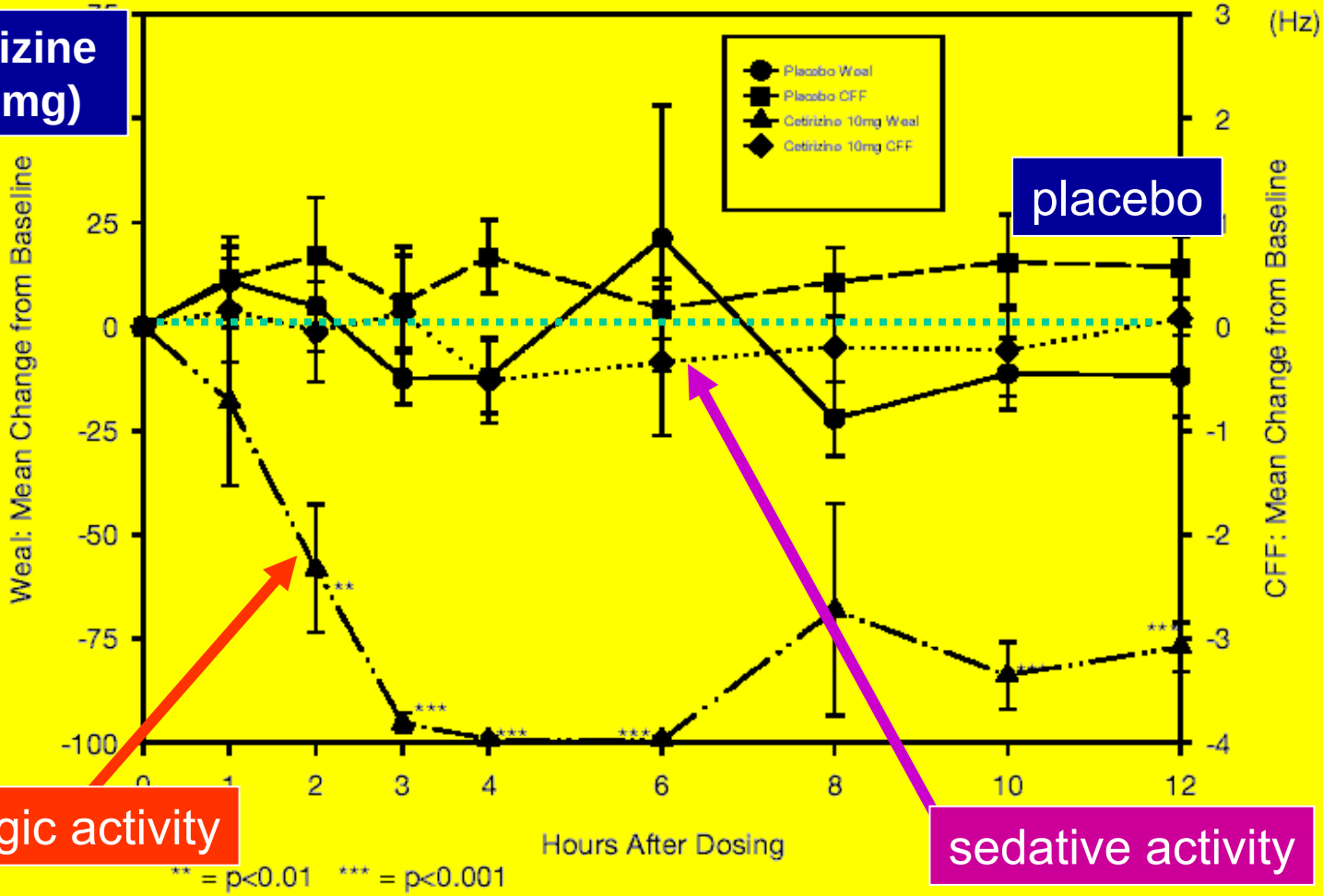


Figure 5. Change from baseline: peripheral antihistaminic suppression (weal) with respect to CFF threshold: acute dose cetirizine 10 mg, day 1

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

Dissociation of anti-allergic and sédative activities...

But, beware:

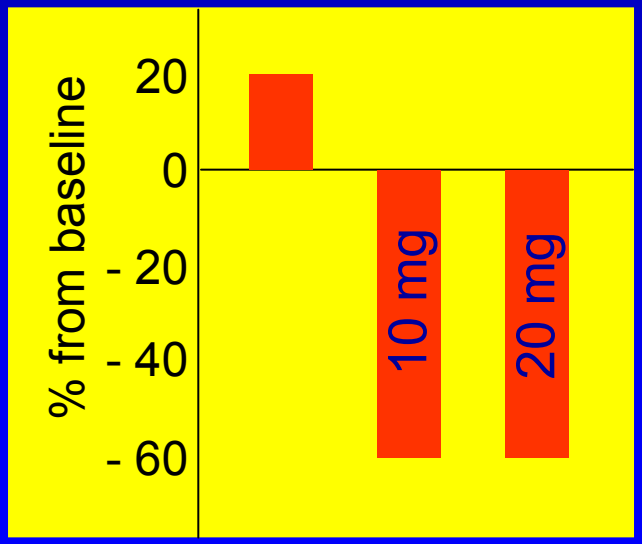
This is all related to dose…

Dissociation of anti-allergic and sedative activities ...

Everything is related to dose…

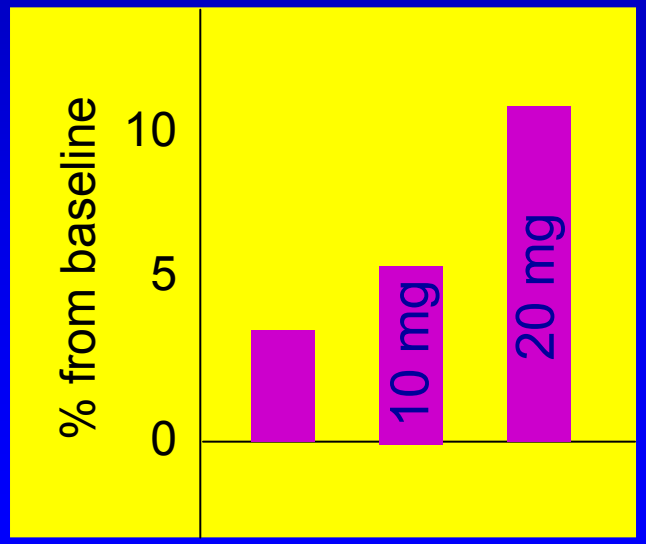
antiallergic activity

placebo | cetirizine



sedative activity

placebo | cetirizine



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

The ideal anti-H1 drug for treating allergy…

Specifications *(Cahier de charges)*

- Low sedative potential
- **Avoiding anti-cholinergic effects…**
  - important for old molecules
    - ➔ 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…

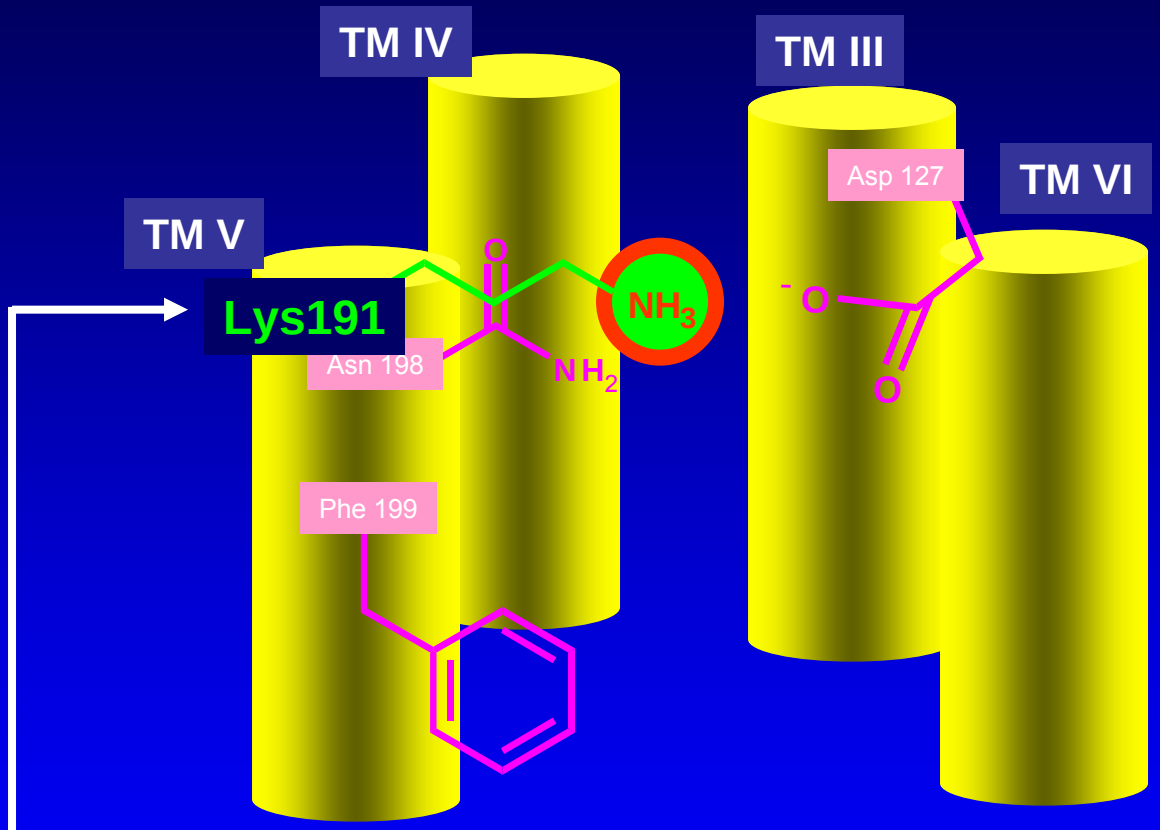
Specifications *(Cahier de charges)*

- Low sedative potential
- Avoiding anticholinergic effects
- **Getting a fast and sustained action**

Moelcular properties of cetirizine

- fast action because no necessity of metabolic activation (>< terfénadine, loratadine…)
- little of no penetration through the blood-brain barrier
- **long occupation of the receptor ....**

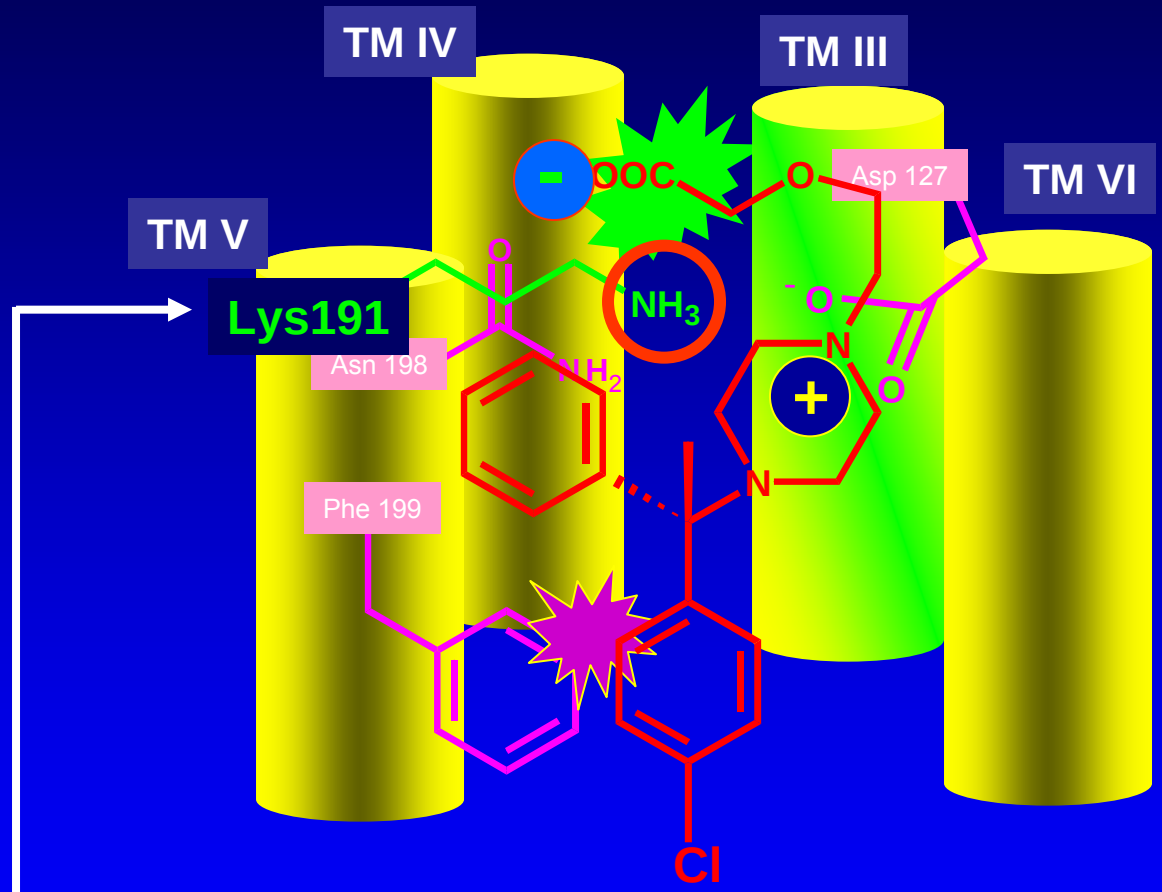
Binding of an H_1 antagonist to the receptor...



Presence of a lysine in position 191

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

Slow release of an antagonist ...



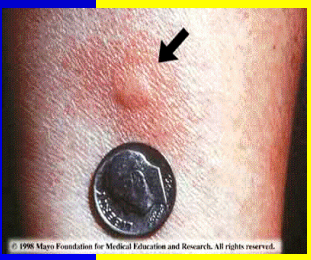
Gillard et al., Mol. Pharmacol. 61:391-399, 2002

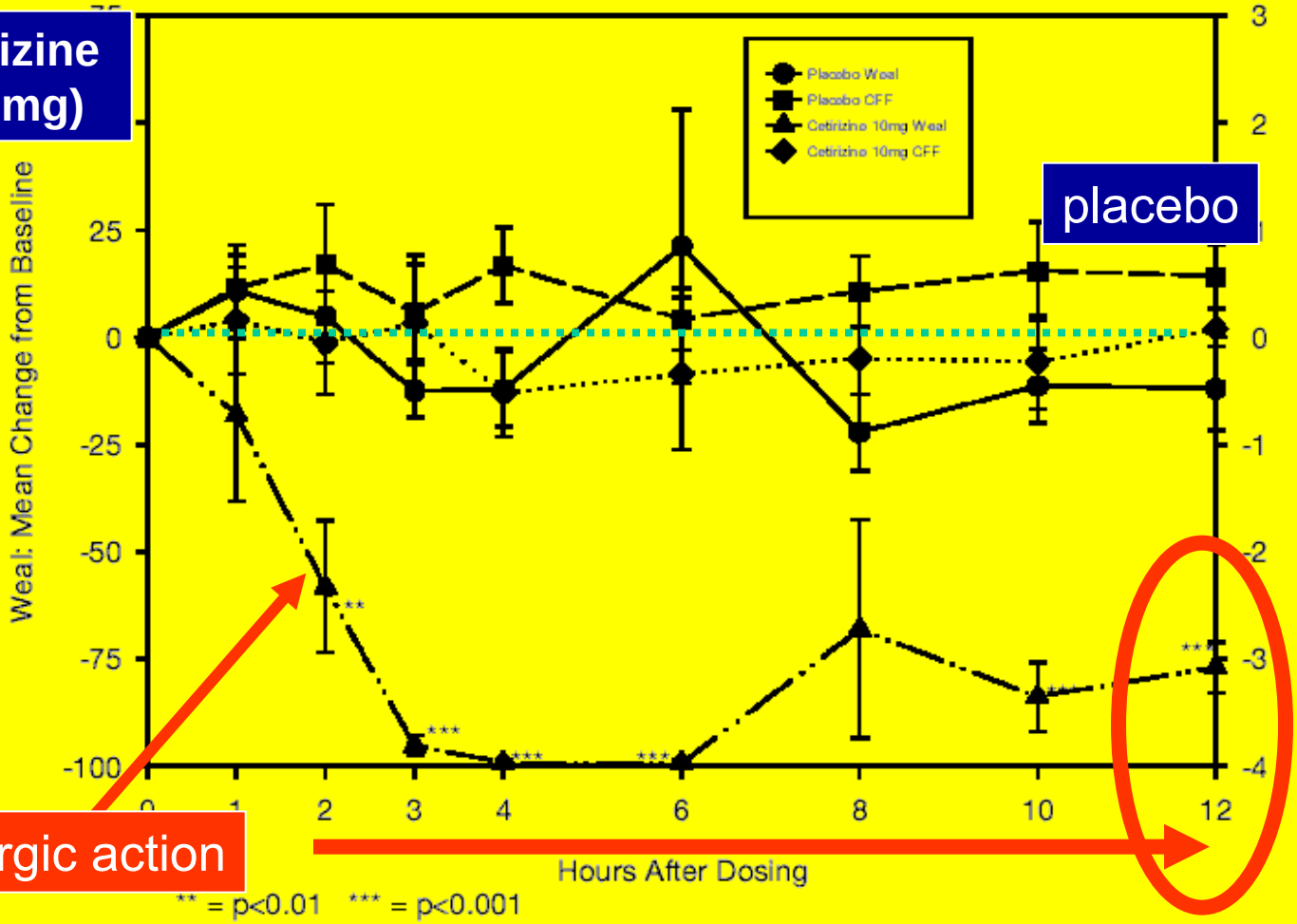
additional electrostatic bound

Slow dissociation and long-lasting action

Prolonged action ...

Cetirizine (10 mg)





placebo

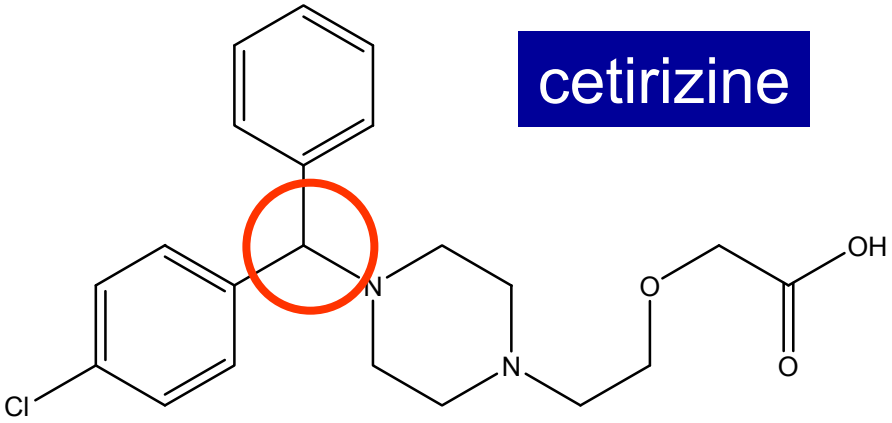
anti-allergic action

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

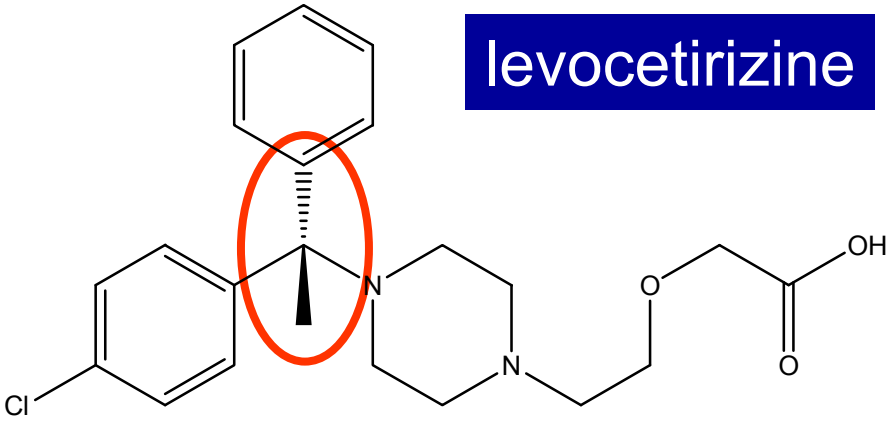
Hindmarch et al., Curr. Med. Res. Opin., 17:241-255, 2001

Cetirizine and levocetirizine....

cetirizine

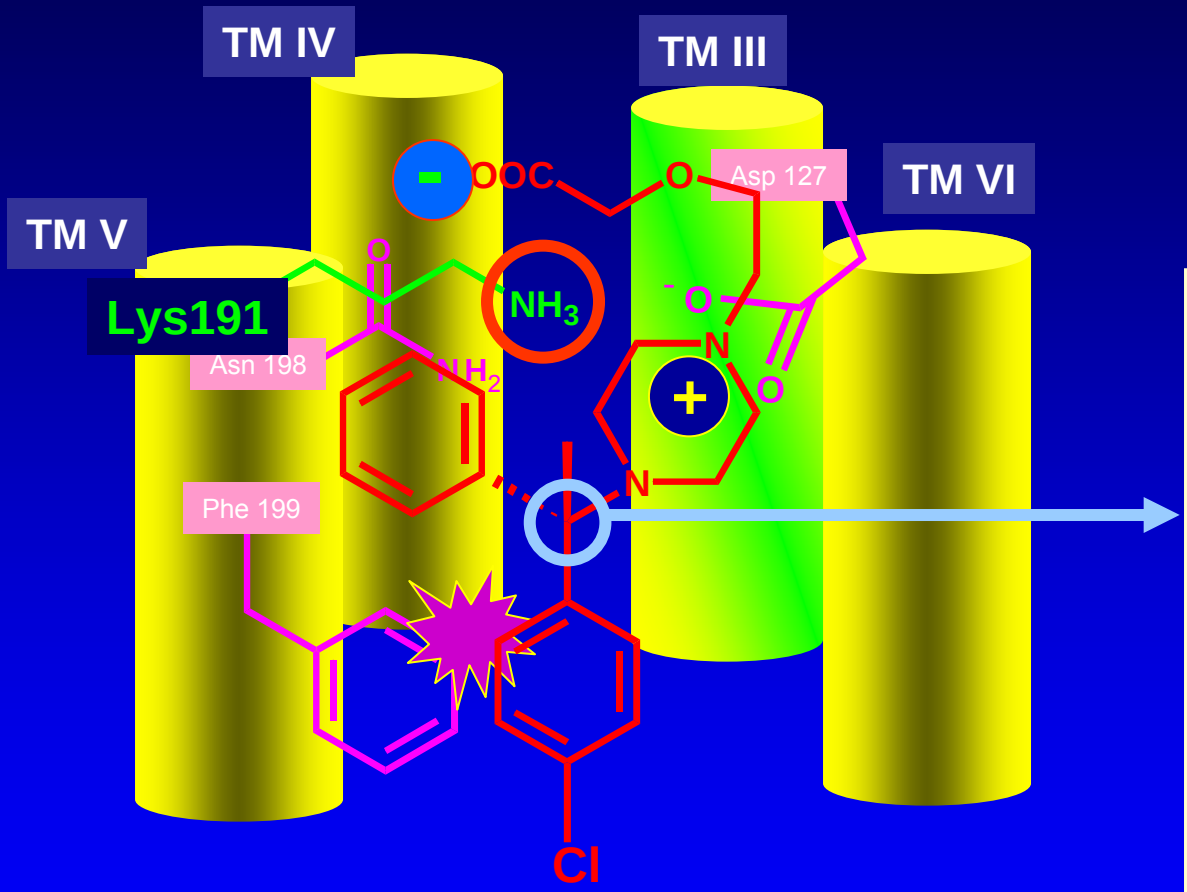


levocetirizine



Acetic acid, 2-[2-[4-[(R)-(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-

Optic isomers and binding to the receptor …



The correct configuration of this C (linking the two hydrophobic groups and the piperazine) is critical for a correct **positioning**, and, thereby, for **activity**

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

0026-895X/02/6102-391–399$3.00
MOLECULAR PHARMACOLOGY

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 H_1 Histamine Receptors: Contribution of Lys^{191} and Thr^{194}

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

disponible sur i-campus

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**

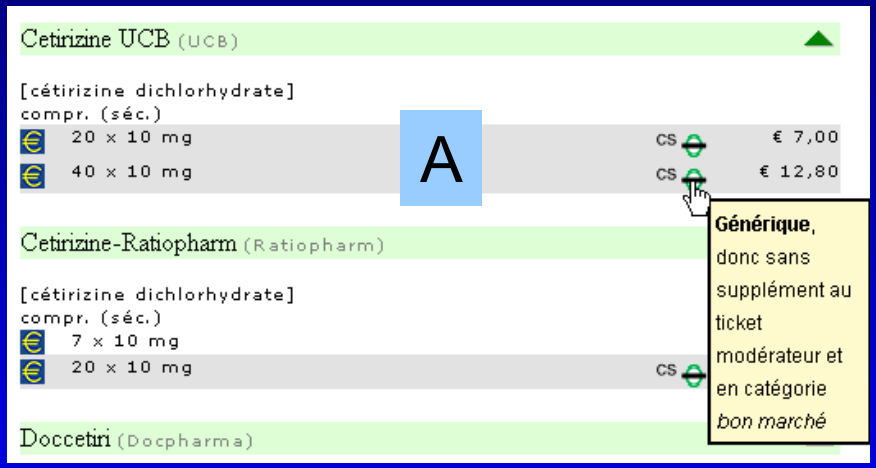
Et pour la suite ...

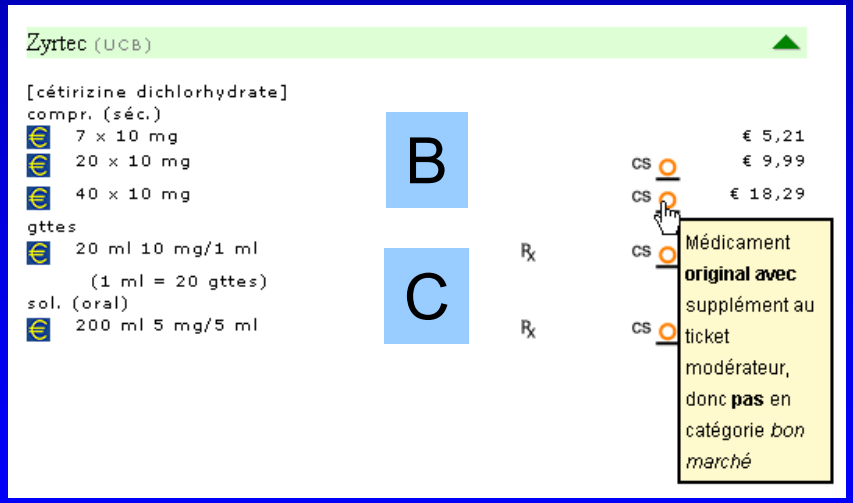
Sur quel point, selon vous, le pharmacien doit-il être particulièrement bien informé par la firme XXX à propos de YYY qui est en vente sans prescription ?

- 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 … ?





Et pourquoi C est-il sous prescription ?

Et voyons les applications ...