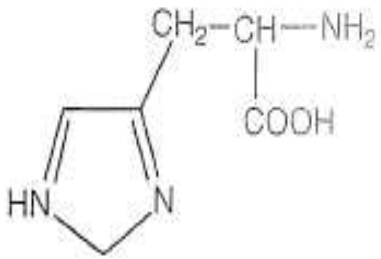
Traitements des allergies et anti-histaminiques

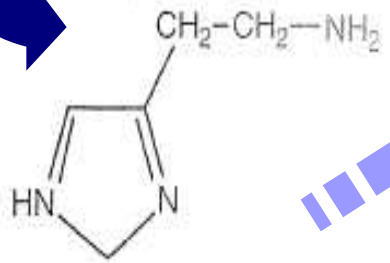
Histamine



L-histidine

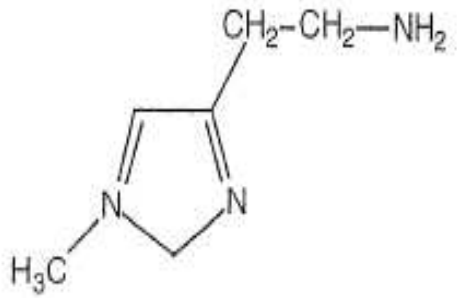
L-Histidine décarboxylase

tritoqualine



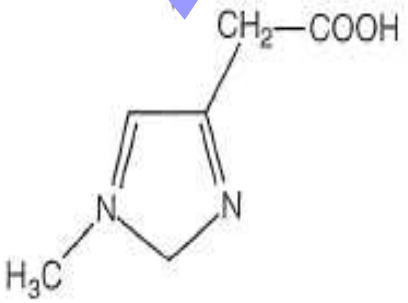
L-histamine

N-méthyl-transférase



N-méthyl-histamine

MAO-B



Acide-N-méthyl-imidazole-acétate

Anaphylaxie …histamine

1901/1902 : Anaphylaxie

Hypersensibilité de type I

1910 : synthèse de l'histamine à partir d'histidine

→1926 : l'histamine est isolée à partir des tissus

→L'histamine induit une contraction de l'utérus
→ L'histamine induit une vasodilatation
→ L'histamine induit des effets semblables à ceux observés chez des animaux "sensibilités"

"Histos" = tissus

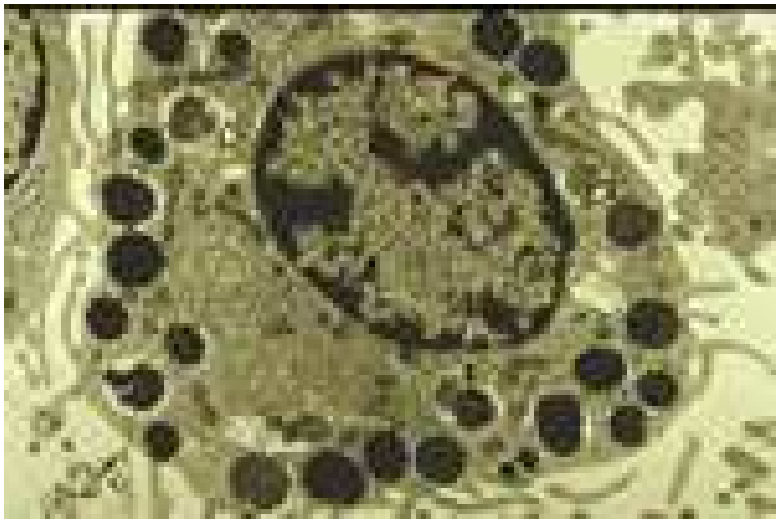
Les tissus cutanés libèrent une substance aux effets similaires à ceux de l'histamine après un contact avec un antigène

Principaux effets de l'histamine

- **mastocytes**
- basophiles

Zones de lésions potentielles :
peau, nez, bouche, pieds,
surface interne de l'organisme,
endothélium vasculaire
+ poumons!

- neurones histaminergiques → SNC
- cellules entérochromaffines →tractus GI



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Fonctions Physiologiques:

Prolifération cellulaire
Hématopoièse
Développement embryonnaire

Mémoire,
cycle veille/sommeil
Rythmes alimentaires
Balance énergétique
Régulation CV

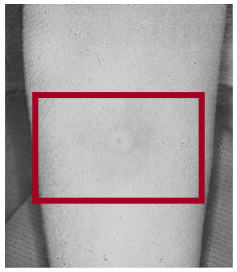
Sécrétion acide estomac

Réactions pathologiques :

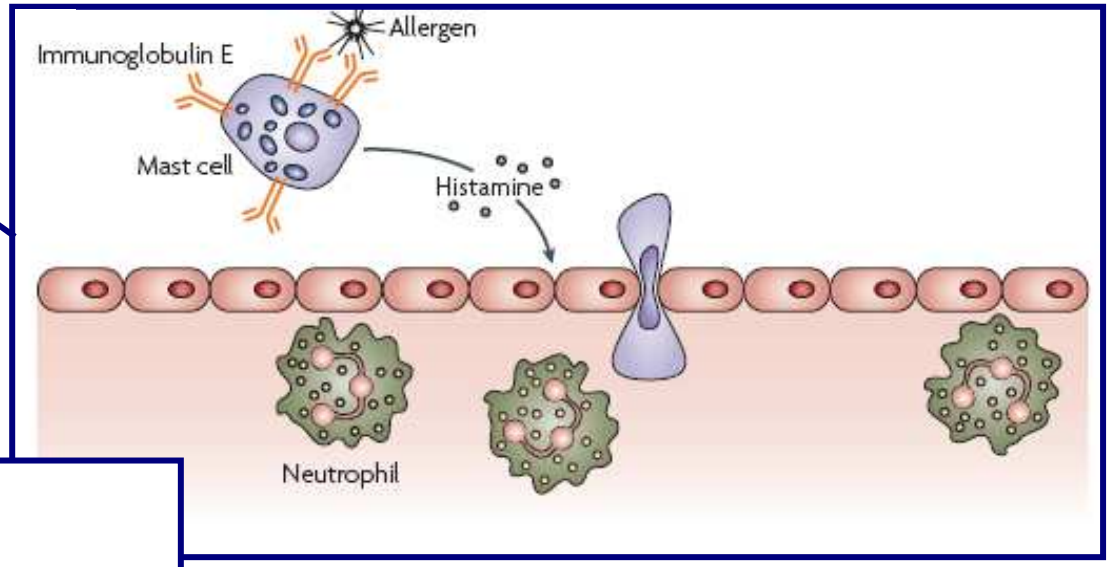
Rhinites/ conjonctivites allergiques
Bronchoconstriction
Crampes
Diarrhées
Réactions cutanées (démangeaisons, …)
Inflammation chronique

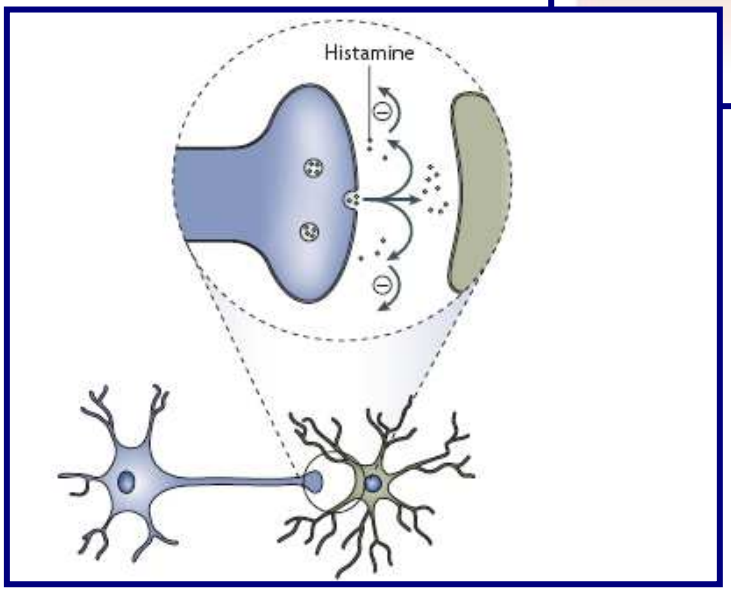
Principaux effets de l'histamine

Vasodilatation
↗ Perméabilité capillaire



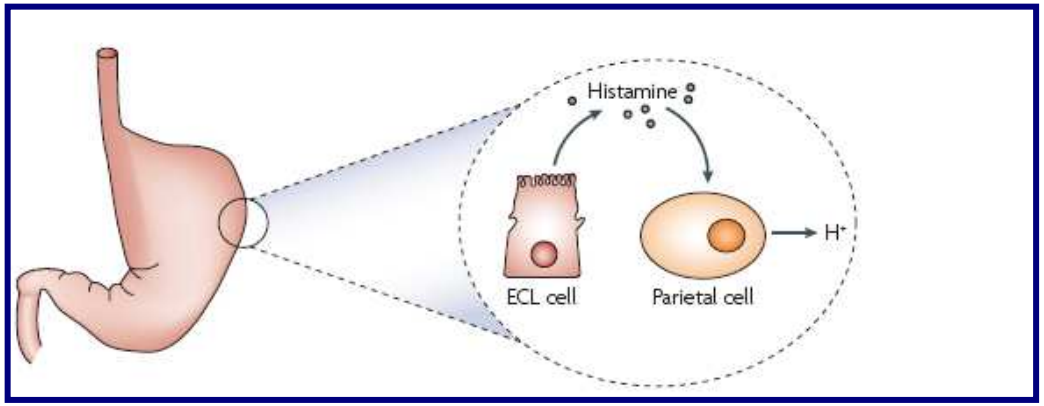
(↗ bronchoconstriction)



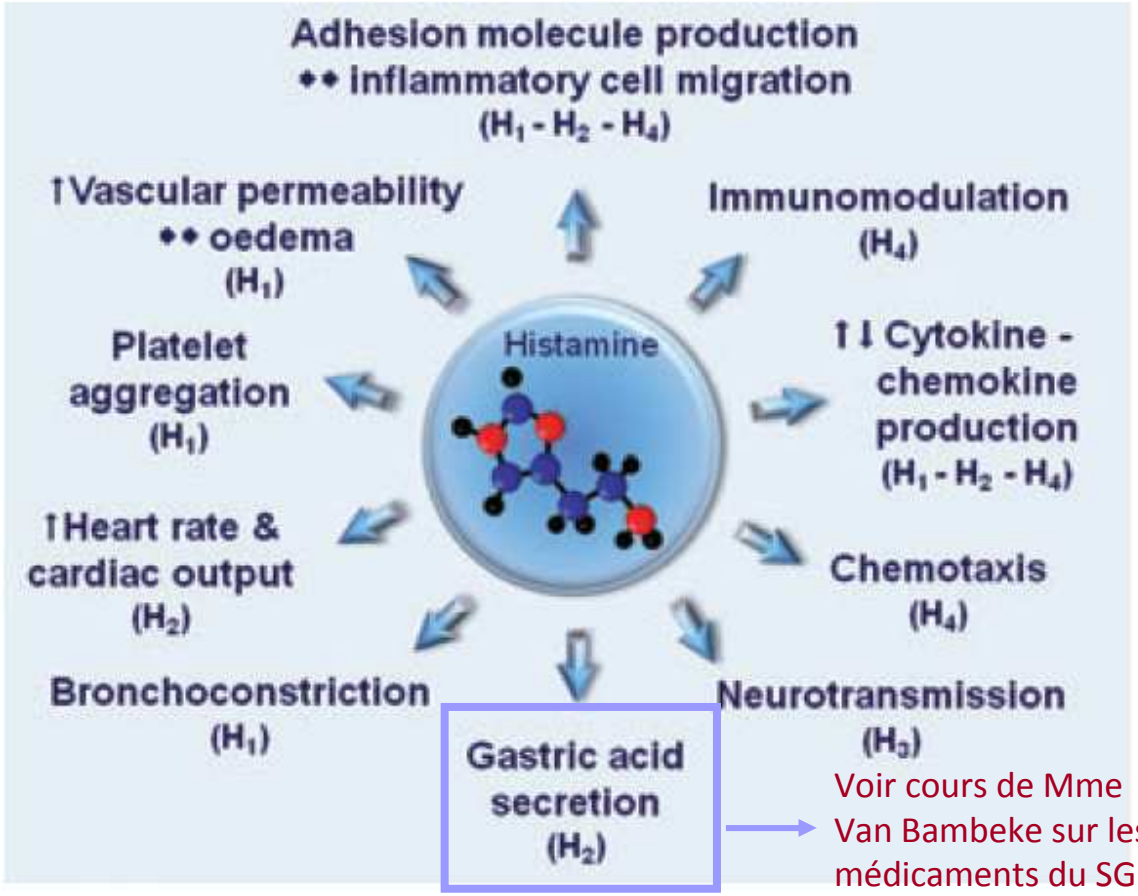


neurotransmission

Sécrétion acide de l'estomac



Principaux effets de l'histamine



Voir cours de Mme Van Bambeke sur les médicaments du SGI

Figure 1 Indicative major effects exerted by histamine. The predominant histamine receptors, designated H_1, H_2, H_3 and H_4, eliciting the effects are shown in parentheses.

British Journal of Pharmacology (2009), 157, 24–33
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Table 1 | **Comparison of different histamine receptors***

Characteristic	H_1	H_2	H_3	H_4
Best characterized function	Acute allergic reactions	Gastric acid secretion	Neurotransmitter modulation	Immunomodulator
G-protein coupling	$G\alpha_q$	$G\alpha_s$	$G\alpha_{i/o}$	$G\alpha_{i/o}$
Major signalling pathway	Increases in Ca^{2+}	Increases in cAMP	Inhibition of cAMP	Increases in Ca^{2+}
Histamine pK_i	4.2	4.3	7.8	8.1
Diphenhydramine pK_i	7.9	>10,000‡	<5	<5
Loratadine pK_i	6.8	ND	ND	<5
Cetirizine pK_i	8.0	ND	ND	<5
Fexofenadine pK_i	8.3	ND	ND	<5
Ranitidine pK_i	<4	7.1	<5	<5
Cimetidine pK_i	<5	6.2	<5§	<5
Thioperamide pK_i	<5	<4	7.3	7.2
JNJ 7777120 pK_i	<5	>4.5	5.3	8.4

*All pK_i values (negative log of the apparent dissociation constant) are from REF. 39 except where noted. ‡From REF. 195. §From REF. 34. cAMP, cyclic AMP; ND, not determined.

Les récepteurs à l'histamine

Table 1. Histamine receptors (HR), expression, coupled G-proteins and activated intracellular signals

Histamine receptors	Expression	Activated intracellular signals	G-proteins
HR1	Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, macrophages, DC, T and B cells	Ca^{2+}, cGMP, phospholipase D, phospholipase A_2, NFκB	$G_{q/11}$
HR2	Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, macrophages, DC, T and B cells	Adenylate cyclase, cAMP, c-Fos, c-Jun, PKC, p70S6K	$G\alpha_s$
HR3	Histaminergic neurons, eosinophils, DC, monocytes, low expression in peripheral tissues, macrophages – unknown	Enhanced Ca^{2+}, MAP kinase, inhibition of cAMP	$G_{i/o}$
HR4	High expression on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, DC, T cells, basophils, mast cells, low expression in nerve cells, hepatocytes peripheral tissues, spleen, thymus, lung, small intestine, colon and heart, macrophages – unknown	Enhanced Ca^{2+}, Inhibition of cAMP,	$G_{i/o}$

DC, dendritic cells; PKC, protein kinase C.

Clinical & Experimental Allergy, **39**, 1786–1800
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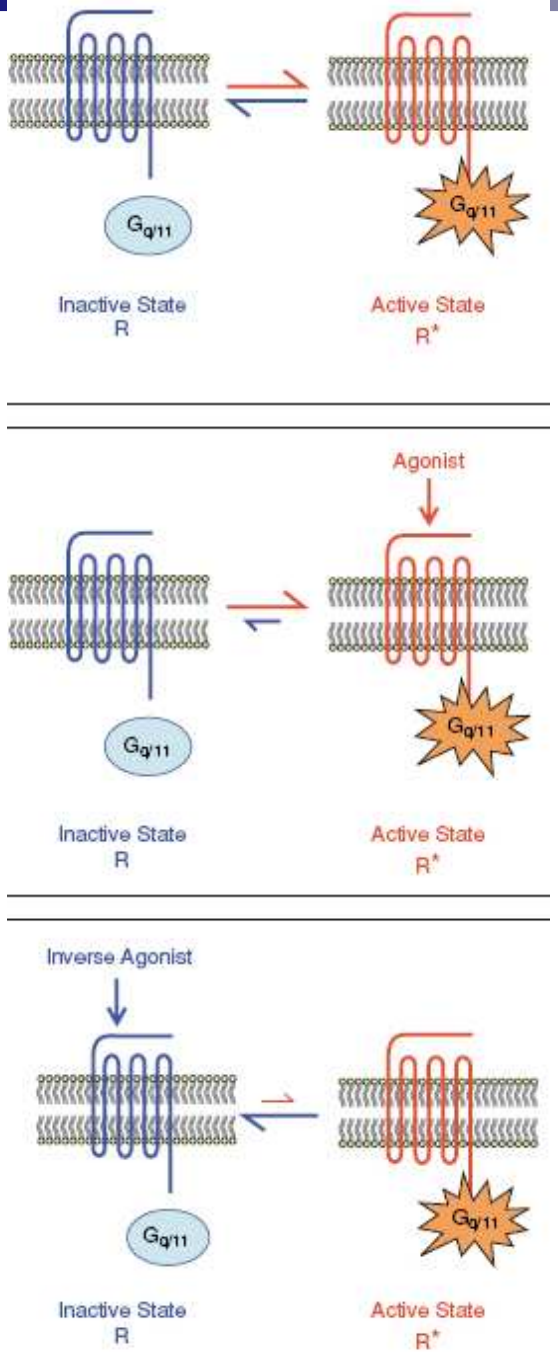
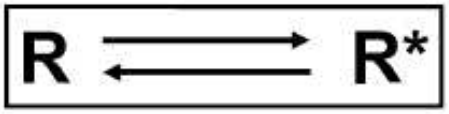


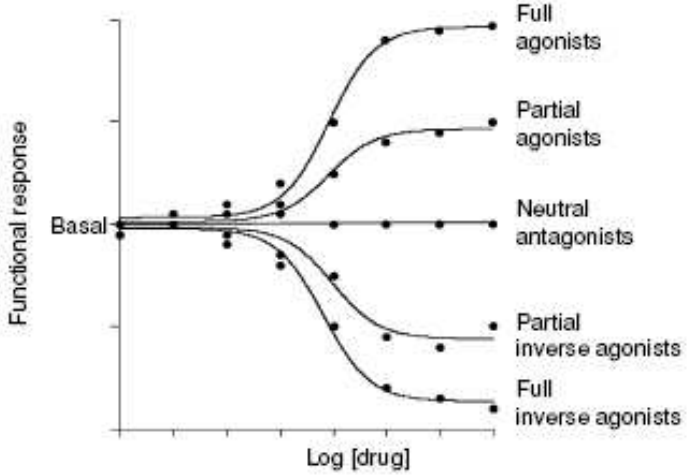
Les 4 récepteurs à l'histamine montrent une activité constitutive. (Ex : l'expression du récepteur h-H1 dans des cellules COS → l'activation de la phospholipase C même en absence de ligand; cette réponse est inhibée par les anti-H1 spécifiquement.)

→ Notion d'agonisme inverse

→ anti-histamine plutôt que "antagoniste de l'histamine"

→ Conséquences sur l'expression des récepteurs ou le couplage lors de l'utilisation d'agonistes inverse ou d'antagonistes neutres?????

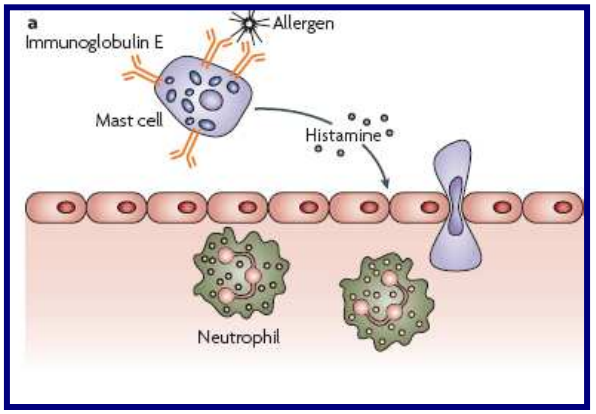




→ Ex : tripolidine

→ Ex : mepyramine

La réaction allergique (rappels)



→ Réactions d'hypersensibilité de type I :

- réactions anaphylactiques ou atopiques
- hypersensibilité immédiate à IgE
- lymphocytes, mastocytes, basophiles

→Phase silencieuse : 1ère rencontre avec l'antigène→ sensibilisation
→Contact secondaire avec l'allergène → phase réactionnelle

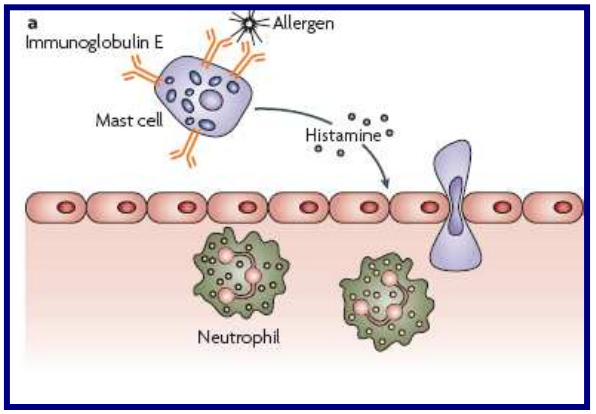
Vs:

Réaction d'hypersensiblité de type II: (toxicité/neutralisation; IgM, complément, lyse ou phagocytose)

Réaction d'hypersensiblité de type III (formation de complexes immuns, IgM, IgG, complément)

Réaction d'hypersensiblité de type IV (médiation cellulaire; libération de cytokines)

La réaction allergique (rappels)



→ Réactions d'hypersensibilité de type I :

Systémique
→ choc anaphylactique

Voies respiratoires
→ rhinites allergiques
- saisonnières
- annuelles

→ asthme

Yeux
→ conjonctivite allergique

Peau
→ urticaire
→ (dermatite de contact → hypersensibilité retardée)

Allergènes classiques:
Pollen,
Acariens
Poils et protéines animales
Aliments (arachides, kiwi, fraises,…)
△ Allergies aux protéines du lait >< intolérance au lactose
Latex
Venims
…

Rôle majeur du récepteur H1

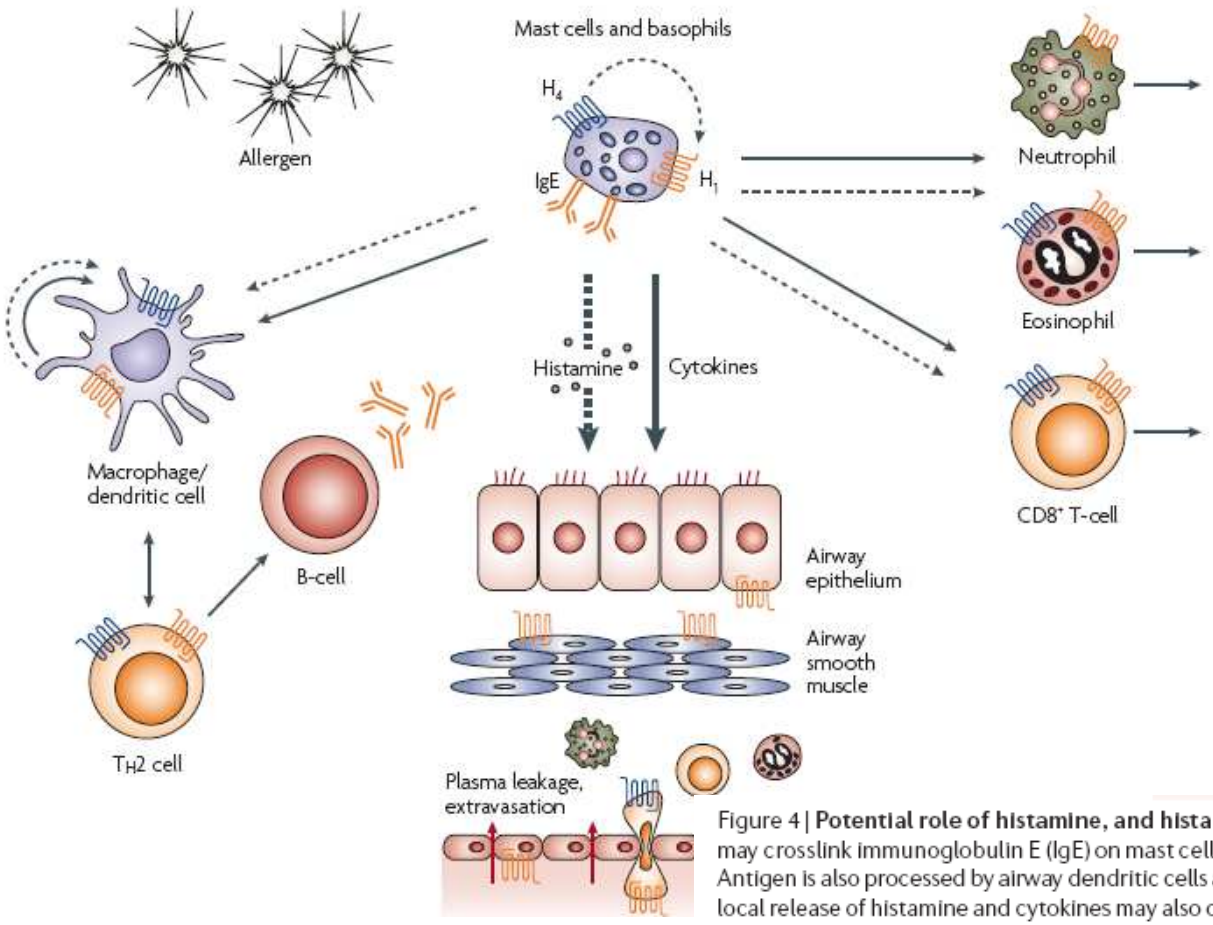
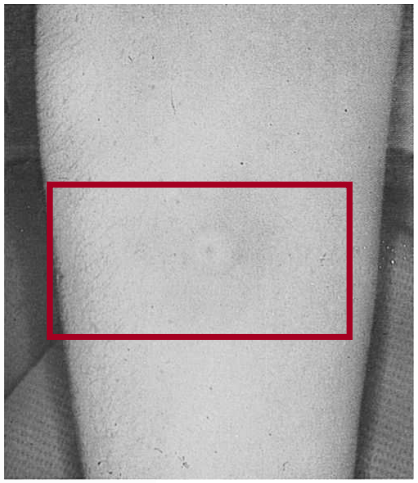
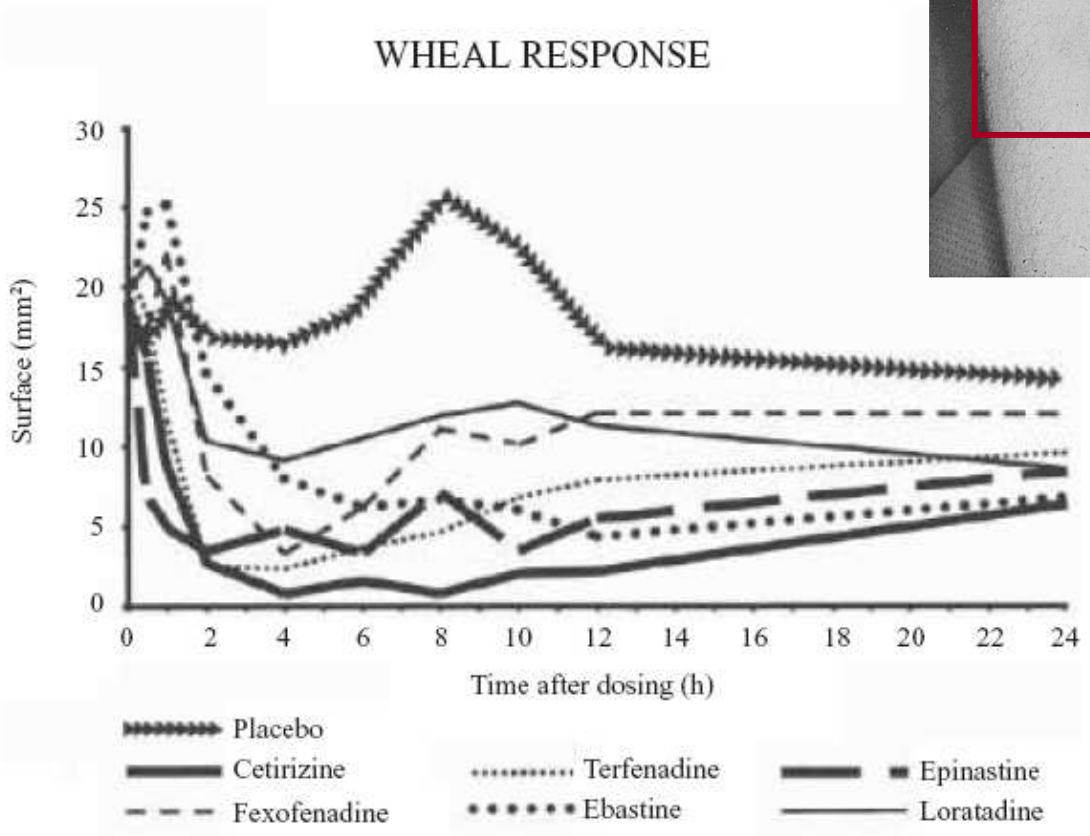


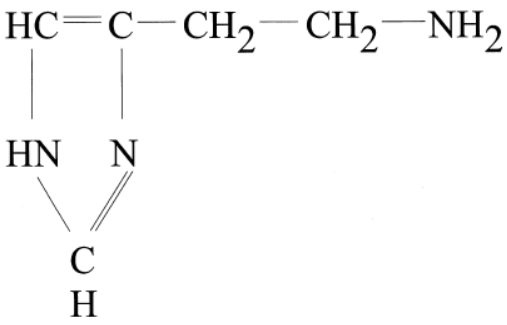
Figure 4 | **Potential role of histamine, and histamine H_1 and H_4 receptors in asthma.** Allergen entering the airways may crosslink immunoglobulin E (IgE) on mast cells (or basophils) to release histamine, lipid mediators and cytokines. Antigen is also processed by airway dendritic cells and macrophages for presentation to T-helper cells. During this process local release of histamine and cytokines may also occur. Resultant histamine from these processes can act on a variety of cells and at different levels. Histamine can facilitate the recruitment of inflammatory cells by direct chemotaxis of additional dendritic cells, eosinophils and mast cells to the airways via action at H_4 receptors (blue), while also aiding the chemotactic and inflammatory process through effects at H_1 receptors (orange) on the airway epithelium and vascular endothelium. Release of cytokines, such as interleukin 8 (IL8), from the airway epithelium and increased vascular permeability in response to H_1 receptor activation enrich the inflammatory milieu. Constriction and proliferation of airway smooth muscle by H_1 receptors also contributes to the asthma phenotype. Histamine has diverse effects on the activation of leukocytes by H_1 and H_4 receptors. Complex autocrine and paracrine processes in response to dendritic cell histamine and cytokine release control the priming and education of T cells, via cytokines that are released from dendritic cells in response to H_1 and H_4 receptor activation, during antigen presentation. Histamine may additionally affect the cytokine release from $CD8^+$ cells by H_4 receptors and from mast cells, eosinophils and neutrophils through multiple histamine receptor activity. Histamine effects are represented by dashed black arrows, cytokine effects by solid black arrows, and plasma extravasation by red arrows.



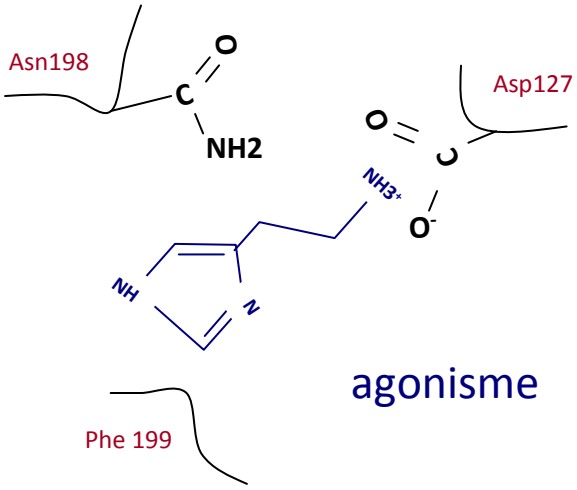


J Investig Allergol Clin Immunol 2006; Vol. 16, Supplement 1: 3-12

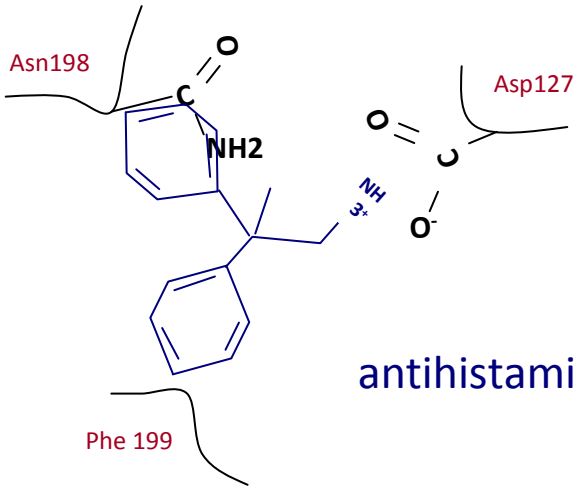
Développement des antihistaminiques



Histamine



agonisme



antihistamine

Antihistamines

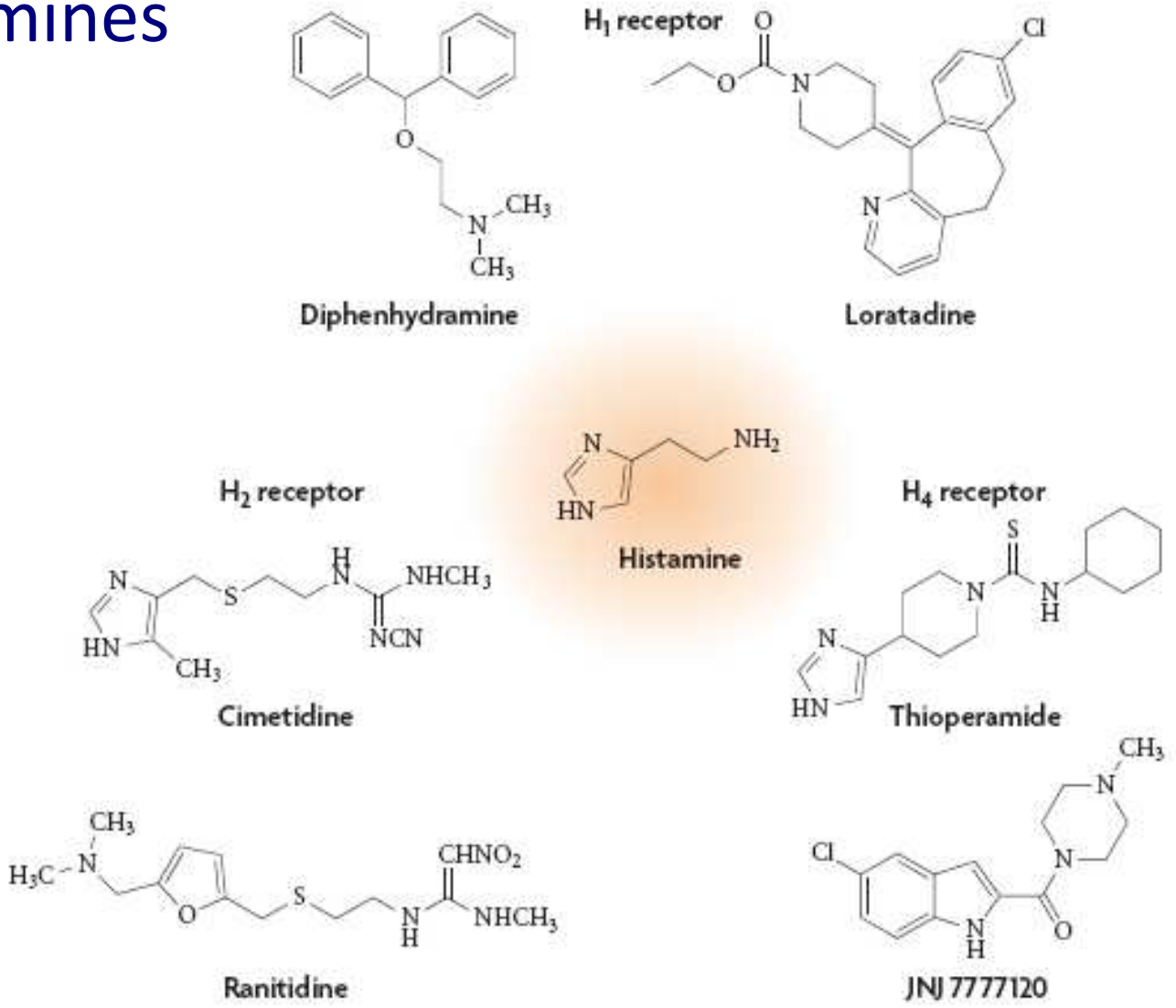
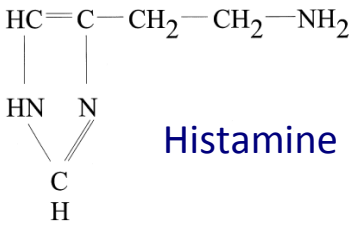


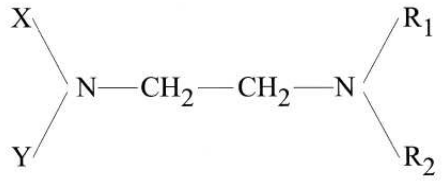
Figure 2 | Representative histamine receptor ligands.

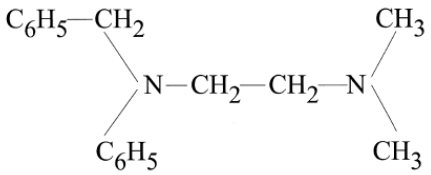
Développement des antihistaminiques



Histamine

ethylenediamine





Antergan → 1942

Antergan : 1er antihistaminique à avoir été utilisé chez l'homme

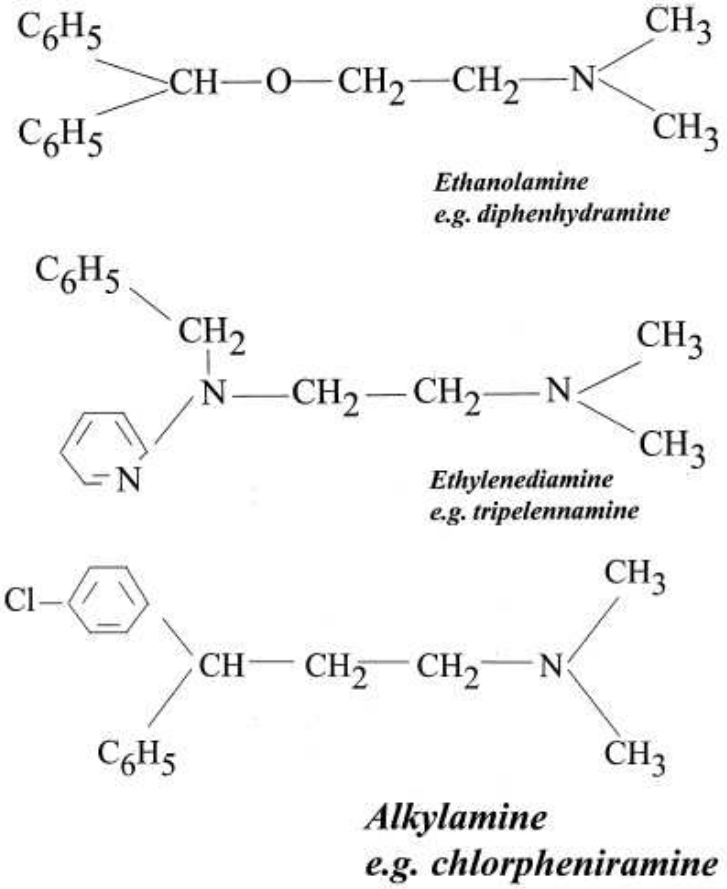
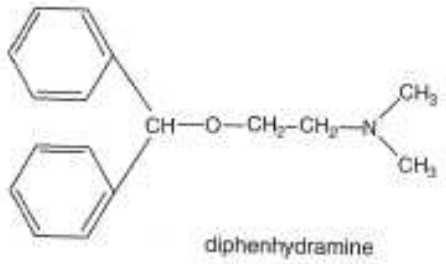


Fig. 15. Structure of representative H_1 antagonists.

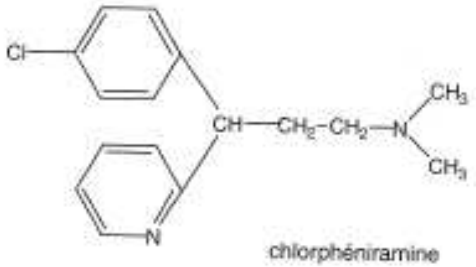
Développement des antihistaminiques

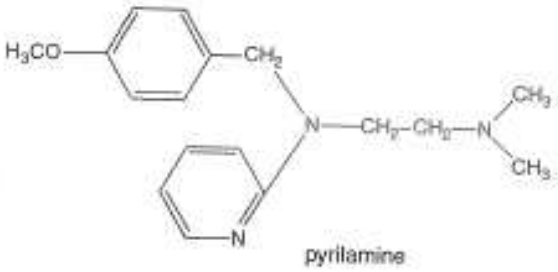
• somnolence
•Effet antinaupathique

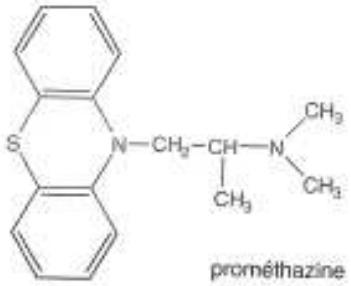


R Calm®
Nustasium®

Dexchlorpheniramine : Polaramine ®







Phenergan®

Figure 19.5 – **Antagonistes H1 de première génération.**

Rôle possible dans la mort subite du nourrisson

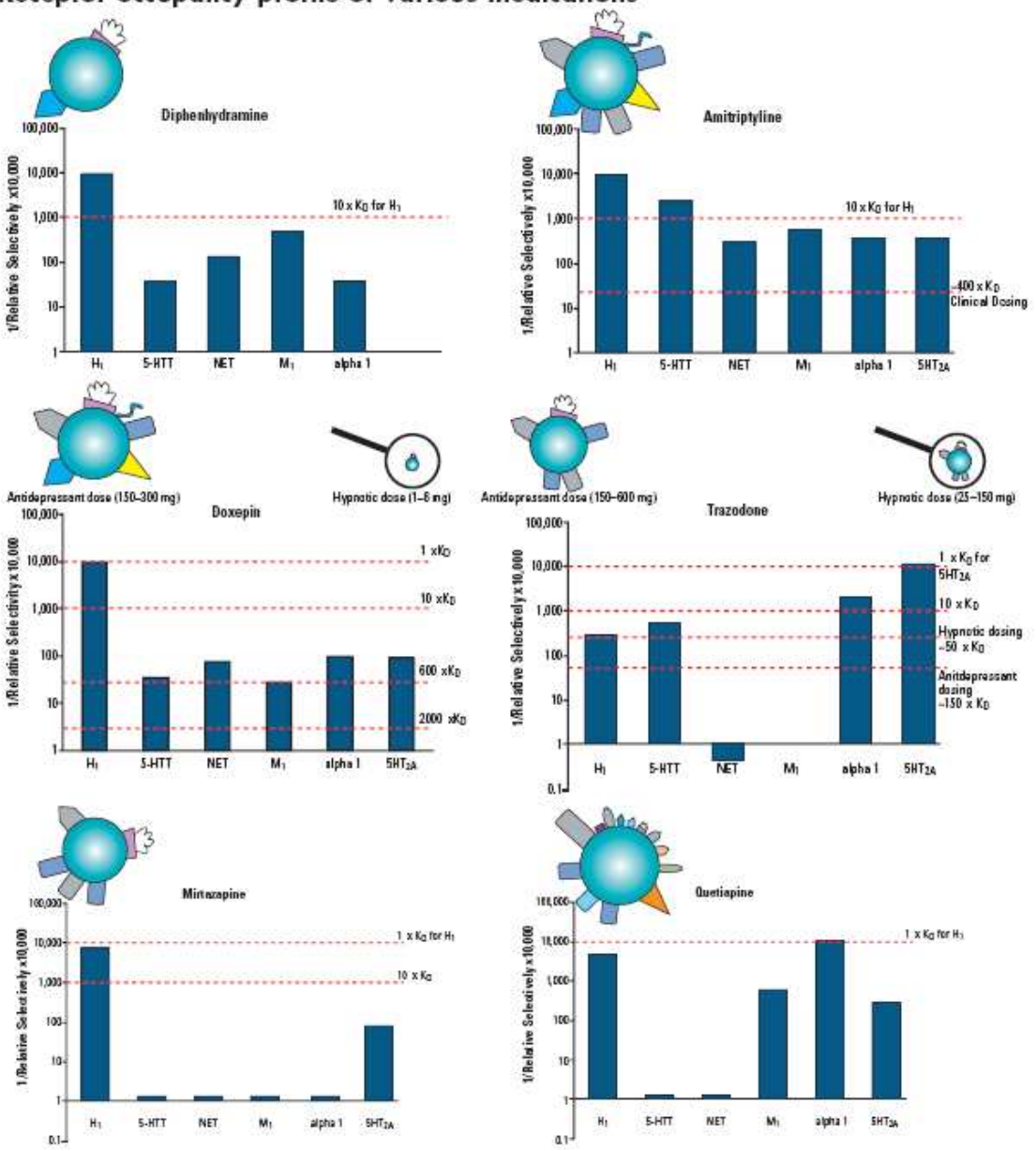
Noyau phenothiazine :
• antiallergique
• sédation
Ses propriétés sédatives sont à l'origine du développement
l'origine du développement des 1er neuroleptique comme la chlorpromazine

Caractéristiques des antihistaminiques de 1ere génération :

- efficaces contre la réaction allergique
- induisent de la somnolence
- effet antinaupathique pour certains

• faible sélectivité pour H1 vs récepteurs dopaminergiques et muscariniques
• passage de la barrière hématoencéphalique

FIGURE 6.
Receptor occupancy profile of various medications



K_D=equilibrium dissociation constant; H=histamine; 5-HTT=serotonin transporter; NET=norepinephrine transporter; M=muscarinic.

Stahl SM. *CNS Spectr*. Vol 13, No 12. 2008.

Pour les antihistaminiques qui passent la barrière hémato-encéphalique

TABLE 1.
Myths About the Clinical Actions of "Antihistamines"

Myth 1: Antihistamines block H_1 receptors, so this is the cause of all their clinical actions
Myth 2: Blocking H_1 receptors at night will cause daytime sedation as well as nighttime hypnotic actions, and these effects will wear off over time.
Myth 3: H_1 receptor blockade causes weight gain

H=histamine.

Stahl SM. *CNS Spectr.* Vol 13, No 12. 2008.

Les antihistaminiques H1 sont responsables de l'efficacité contre l'allergie

Les antihistaminques H1 sont responsables des effets hypnotiques.
En fonction de la dose : effet spécique ou moins.
(pendant la nuit: saturation des récepteurs H1 (agonisme inverse à un moment du rythme circadien où les taux d'histamine sont bas) --> possibilité d'utiliser les anti H1 de 1ère génération à faible dose pour traiter les troubles de sommeil en limitant les effets indésirables ?)

Si plus forte dose : saturation des récepteurs H1 le jour, activité sur les autres sytèmes "veille/sommeil" → risque de sédation diurne, d'effet rebound et de tolérance.

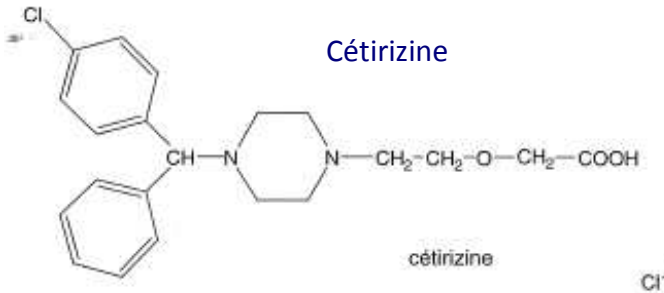
Les effets antihistaminiques H1 ne sont pas responsables des effets anti-dépresseurs

Développement des antihistaminiques

Caractéristiques des antihistaminiques de 2de génération :

- efficaces contre la réaction allergique
- faible passage de la barrière hématoencéphalique → peu ou pas de somnolence
- meilleure sélectivité pour H1

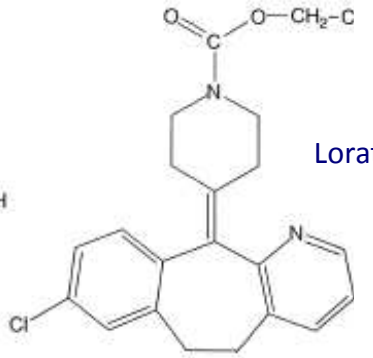
Zyrtec ®
Réactine ®
Hyperpoll ®



Cétirizine

cétirizine

Claritine ®
Rupton ®
Sanelor ®

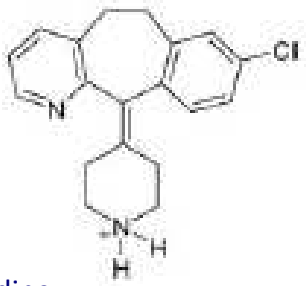


Loratidine

Lévocétirizine (xyzal®)

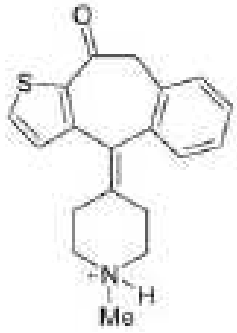
enatiomère de la cétirizine
3ème génération anti H1

Développement des antihistaminiques



Desloratadine

Métabolite de la lorétadine
3ème génération anti H1



Ketotifen

1ère génération

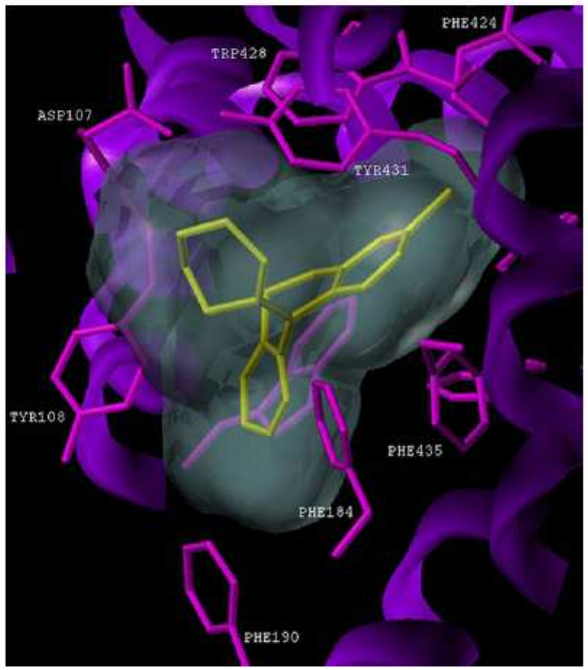


Fig. 9. Binding mode of desloratadine within the active site of HHR1. Residues that are important in forming the active site are coloured violet and labelled. Desloratadine, coloured yellow, is represented in capped stick rendering within its translucent van der Waals surface.

R. Kiss et al. / European Journal of Medicinal Chemistry 39 (2004) 959–967

Table 5. Calculation of PIR-S for all AHs included in review and update

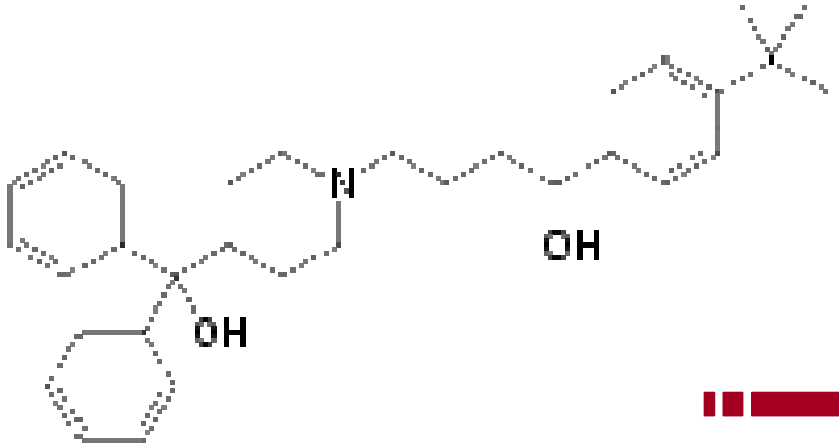
Drug	a	b	c	d	PIR
Acrivastine	0	4	152	155	0.000
Desloratadine	0	5	152	154	0.000
Fexofenadine	0	26	152	133	0.000
Levocetirizine	0	4	152	155	0.000
Mequitazine	0	14	152	145	0.000
Olopatadine	0	1	152	158	0.000
Tazifylline	0	3	152	156	0.000
Loratadine	2	19	150	140	0.184
d-chlorpheniramine	1	6	151	153	0.288
Cetirizine	5	24	147	135	0.331
Azatadine	1	4	151	155	0.405
Ebastine	4	14	148	145	0.440
Mizolastine	3	9	149	150	0.502
Brompheniramine	1	1	151	158	1.023
Cyclizine	1	1	151	158	1.023
Emedastine	1	1	151	158	1.023
Chlorpheniramine	14	8	138	151	1.333
Clemastine	10	4	142	155	1.494
Triprolidine	23	4	129	155	1.875
Promethazine	19	2	133	157	1.973
Temelastine	1	0	151	159	2.053
Dimenhydrinate	2	0	150	159	2.060
Meclizine	2	0	150	159	2.060
Diphenhydramine	37	5	115	154	2.061
Ketotifen	3	0	149	159	2.067
Oxatomide	3	0	149	159	2.067
Rupatadine	4	0	148	159	2.074
Hydroxyzine	15	0	137	159	2.161

a: Number of tests showing 'impairment' with the named AH.
b: Number of tests showing 'no impairment' with the named AH.
c: Number of tests showing 'impairment' with all other AHs.
d: Number of tests showing 'no impairment' with all other AHs.

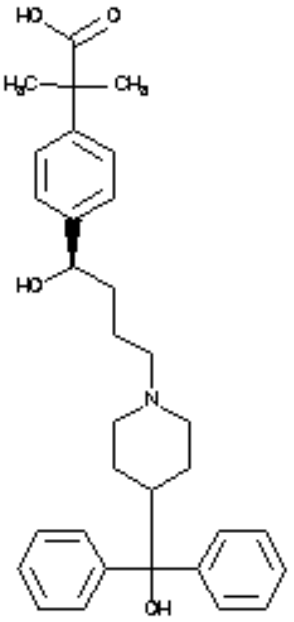
PIR: proportionnal impairment ratio → cognitive and psychomotor impairments

HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2008; 23: 555–570.
Published online 11 July 2008 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.962

Développement des antihistaminiques



cyp3A4

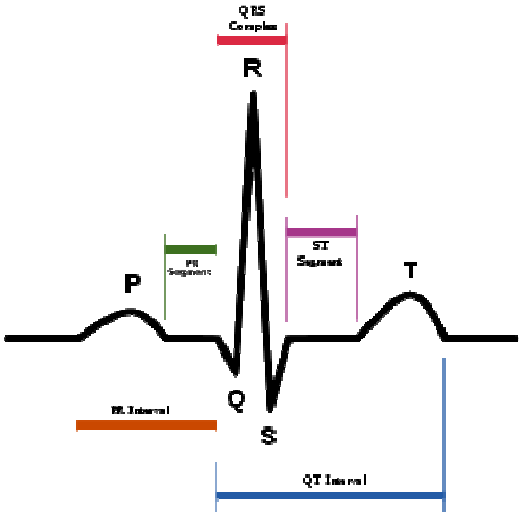


Terfenadine :
Prodrogue inactive
Responsable de l'allongement de l'espace QT

Retirée des marchés

fenofenadine

Métabolite de la terfenadine
3ème génération anti H1



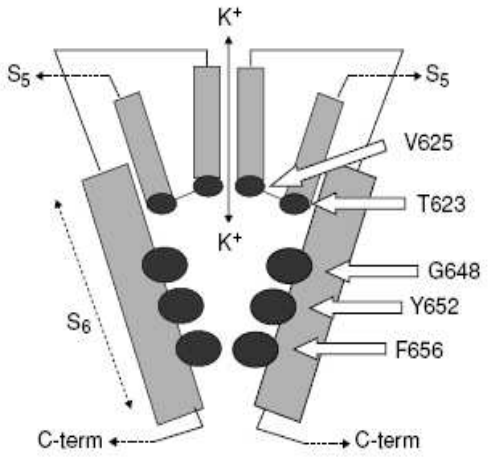


Fig.5. Schematic drawing of the pore region and of the S_6 transmembrane segment of HERG1. Only two of the four channel-forming subunits of HERG1 channels are drawn. The residues T623 and V625 (in the P-region) and G648, Y652, and F656 (in S_6), which appear to be crucial for drug binding to HERG1 channels, are highlighted. In particular, terfenadine binding has been shown to be influenced by mutations at the

Progress in Cardiovascular Diseases, Vol. 45, No. 5, (March/April) 2003: pp 415-427

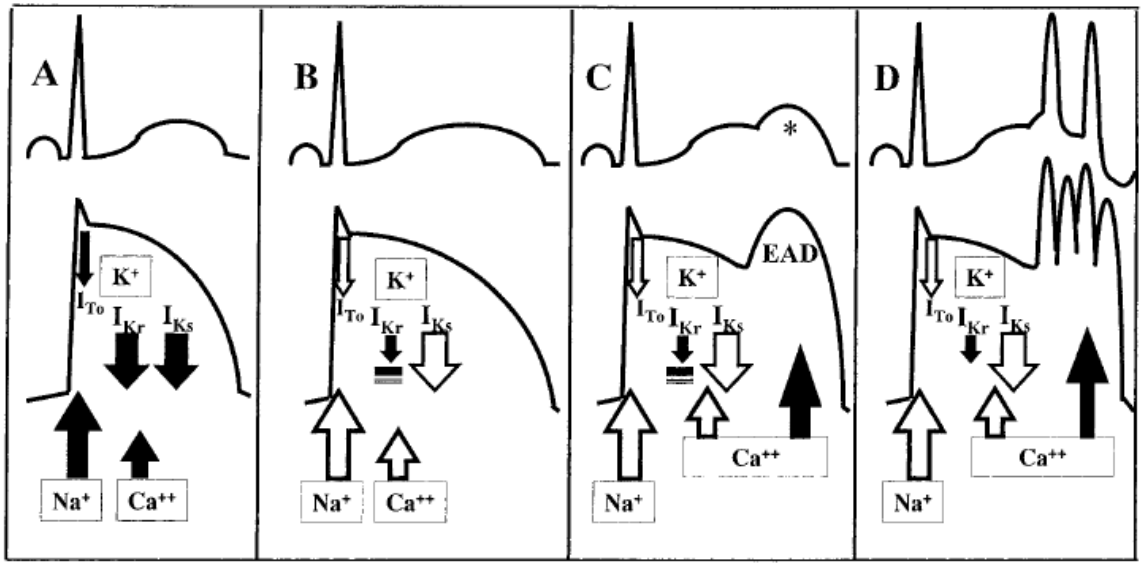


Fig 2. (A) shows the normal action potential and the corresponding electrocardiogram. The main ion currents are shown. ↑, ion-currents entering the cell (raising the action potential); ↓, outward currents (shorten the action potential). The net balance of inward and outward currents dictates the duration and contour of the action potential, and, consequently, the QT interval. (B) Malfunction of rapid delayed-rectifier potassium currents (I_{Kr}) as occurs in the drug-induced LQTS. The impaired outflow of potassium results in a net excess of inward current and prolongs the action potential. (C) The alteration in action potential recruits additional channels that are voltage dependent (calcium channels), leading to further inward current. *This further raises the action potential, creating EADs that can be seen on the surface electrocardiogram as tall U waves. (D) Some of the EADs reach threshold amplitude and trigger extrasystoles. I_{TO} = transient outward potassium current; I_{Kr} and I_{Ks} = rapid and slow delayed rectifier potassium currents, respectively. Modified from Viskin S.[1]

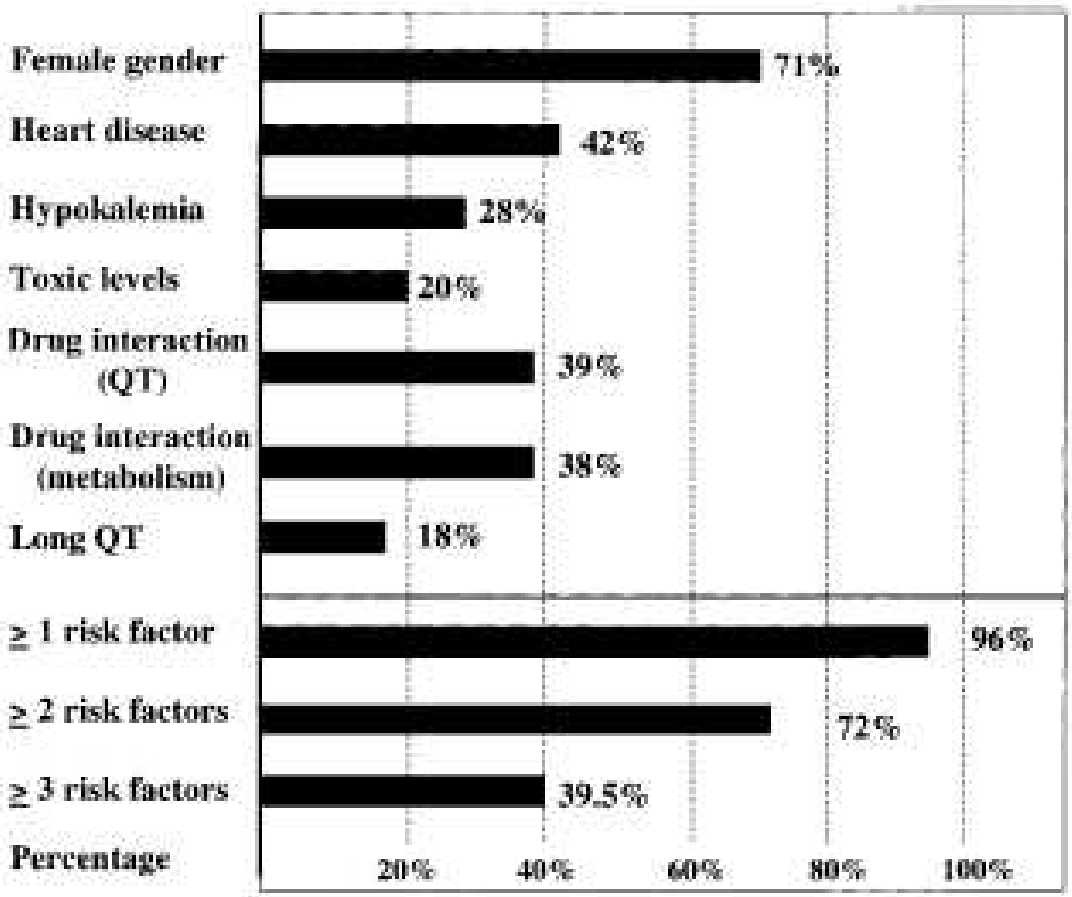


Fig 3. Incidence of easily identifiable risk factors among patients with torsade de pointes triggered by medications with no cardiac indication. Data from 229 published cases.[28] Heart disease, myocardial infarction or significant valvular or hypertrophic heart disease; toxic levels, drug toxicity caused by dosages above recommended doses or by impaired liver or kidney metabolism; drug interaction (QT), treatment with 2 or more drugs that impair myocardial repolarization; drug interactions (metabolism), treatment with one drug that impairs the metabolism of a QT prolonging medication; long QT, patients with a prolonged QT interval before drug therapy, a history of familial long QT syndrome, or a previous episode of drug-induced torsade de pointes.

Table 1. Drugs That Prolong the QT Interval and May Cause Torsades de Pointes

Antiarrhythmic drugs
- Class 1A
  - Quinidine,* disopyramide,* procainamide*
- Class III
  - Sotalol,* d-sotalol,† amiodarone,‡ butilide,* almokalant,† dofetilide*
- Class IV
  - Bepridil†

Non antiarrhythmic Drugs
- Antibiotics
  - Macrolides (erythromycin,‡ clarithromycin§), clindamycin,‖ trimethoprim- sulfametoxazole,‖ quinolones (grepafloxacin,† sparfloxacin,† moxifloxacin,‡ gatifloxacin,‡ levofloxacin,§), amantadine,‖ pentamidine,‡ imidazoles (fluconazole and ketoconazole),‡ chloroquine,§ quinine,‖ halofantrinee§
- Histamine$_1$, receptor antagonists
  - Terfenadine,†‡ astemizole,†‡ fexofenadine‖
- Serotonin receptor antagonists
  - Ketanserine‡
- Serotonin reuptake inhibitors
  - Fluoxetine,‖ zimeldine‖
- Diuretics
  - Indapamide,‡ triamterene‡
- Psychiatric
  - Antidepressants (tetra/tricyclic),§ antipsychotic (thioridazide‡ and other phenothiazines, haloperidol,‡ sertindole,‡ olanzapine‖), droperidol‡
- Cholinergic agonists
  - Cisapride,‡ acetylcholine,** terodiline† (urinary incontinence), organophosphates (insecticides, nerve gas)‖
- Inotropics
  - Amrinone,§ milrinone§
- Other drugs
  - Sildenafil,†† citrate,‖‡‡ vasopressin,‖ carbamezapine,‖,§§ prenylamine† (anti-anginal), probucol† (lipid-lowering) tamoxifen‡ (antiestrogen), sumatriptan‖ (antimigraine)
- Poisons
  - Arsenic,§ organophosphates§ (insecticides, nerve gas)

*Definite association with drug-induced torsades de pointes: the incidence is ≥2% and potassium channel blockade has been shown in vitro.

†The use of this drug was discontinued in some countries owing to the proarrhythmic potential.

‡Same as in *, but with a lower incidence of torsades.

§Several case reports associate this drug with torsades de pointes, the mechanism is not entirely clear.

‖Only isolated reports exist and the association with torsades de pointes is questionable.

¶Toxic dosages of first-generation (sedating) histamine$_1$ blockers (diphenhydramine) moderately increase the QTc but torsade has not been reported.

#Any diuretic may cause hypokalemia and facilitate torsade; also, diuretics increase the risk for torsade during antiarrhythmic therapy (independently of the potassium serum levels); finally, I_{Ks} has been shown in vitro for indapamide and I_{Kr} blockade occurs with triamterene.

**Intracoronary injection of acetylcholine has caused torsade de pointes (the effect was prevented with atropine).

††I_{Kr} blockade has been shown in vitro but its clinical significance during sporadic use of single doses is uncertain.

‡‡Transfusions of large amounts of blood may lead to citrate-induced hypocalemia and QT prolongation

§Only mild QT prolongation has been noted during carbamezapine intoxication.

Modified from Viskin and Roden [38].

NOTE. A continuously updated list of drugs that can cause a long QT syndrome may be found at http://www.torsades.org.

A la recherche d'antihistaminiques de 3ème génération

→ recommendations

Consensus group on new-generation antihistamines (CONGA): present status and recommendations

Clin Exp Allergy 2003; 33:1305–1324

Effets anti-inflammatoires

- Presently, it is not possible to establish what, if any, is the real clinical relevance of the anti-allergic/anti-inflammatory properties described in numerous experimental models. The anti-allergic properties should be demonstrable *in vivo*, in humans, at therapeutic doses and under natural exposure to the offending allergens.
- An antihistamine with anti-allergic properties should be demonstrated to be superior (in humans) to a comparator devoid of such properties.
- Since the major clinical expression of chronic inflammation in the nose is nasal obstruction, anti-allergic/anti-inflammatory properties should affect that symptom in a measurable way. This should be demonstrable especially in persistent rhinitis, where obstruction predominates over histamine-induced symptoms.

Toxicité cardiaque

- Life-threatening adverse cardiac side-effects such as QT prolongation and torsades de pointes ventricular tachyarrhythmias have been described in association with the use of some second-generation antihistamines (astemizole and terfenadine).
- These effects are consequent to direct blockade of a specific class of potassium channels controlling the repolarization phase of the cardiac action potential, and are not related to the blockade of the H1 receptor. Thus, cardiotoxicity by second-generation antihistamines is not a class effect.
- Preclinical and clinical studies of predictive ability of such cardiotoxic effects must be performed before novel molecules enter the market.
- Several pharmacokinetic and pharmacodynamic factors can precipitate the occurrence of the arrhythmic episode; medical practitioners prescribing second-generation antihistamines must be aware of these factors in order to avoid exposing the patient to potential dangerous effects.
- The lack of cardiac toxicity, a feature already present in some second-generation antihistamines, must be retained in the development of novel congeners that enter the market in the future.

sedation

- Three factors define the criteria for what is the 'minimum' acceptable for an antihistamine to be classified as a 'non-sedative' drug:

(i) incidence of subjective sleepiness,
(ii) objective and psychomotor functions
(iii) PET measurement of H1-receptor occupancy.

interactions

With regard to drug–drug interactions, a third-generation antihistamine should ideally:

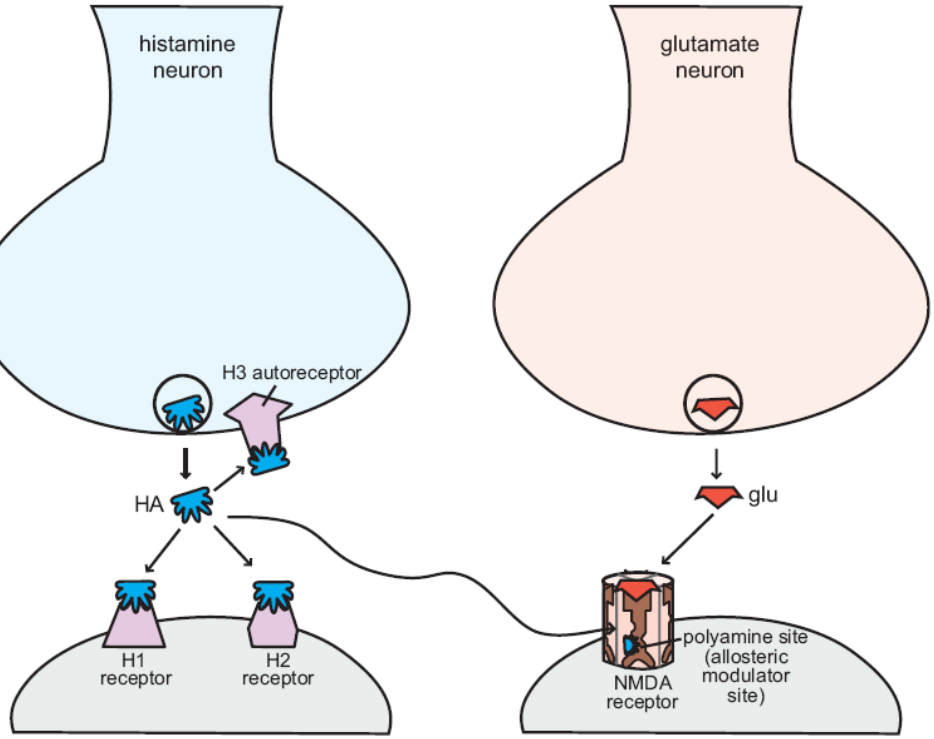
- not affect CYP isoenzyme function
- not displace protein-bound medication
- not affect active transportation mechanism (i.e. P-glycoprotein) important in drug absorption and excretion.

Rapport bénéfices/risques

- The therapeutic index of an antihistamine, defined as its benefit-to-risk ratio, is a more important concept than either potency (as determined in preclinical studies) or efficacy (as determined in clinical trials).
- The second generation, relatively non-sedating H1 antihistamines have a more favourable therapeutic index than the first generation, sedating H1 antihistamines; however, none of the second-generation medication justifies the designation 'third-generation' H1 antihistamine.
- A true third-generation H1 antihistamine will differ radically from existing compounds.

Histamine et ses récepteurs dans le SNC

FIGURE 5.
Histamine receptors



H=histamine; glu=glutamate; HA=histamine; NMDA=*N*-methyl-D-aspartate.

Stahl SM. *CNS Spectr.* Vol 13, No 12. 2008.

H_3 dans le SNC

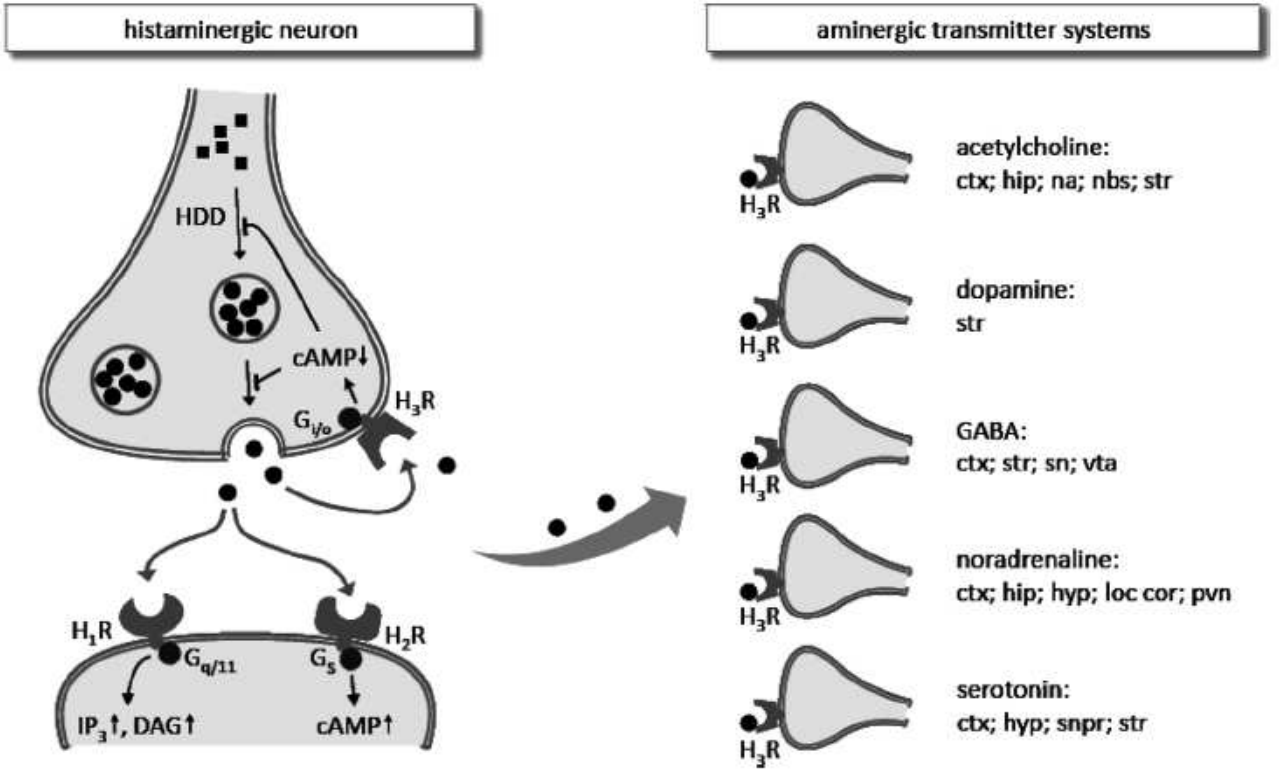


Fig. 2. H_3R Auto- and Heteroreceptors

, histamine H_1 receptor; , histamine H_2 receptor; , histamine H_3 receptor; ●, histamine; ●, G protein. cAMP: cyclic adenosine monophosphate; ctx: cortex; HDD: histamine decarboxylase; hip: hippocampus; hyp: hypothalamus; IP_3: inositol triphosphate; DAG: diacetyl glycerol; loc cor: locus coeruleus; na: nucleus accumbens; nbs: nucleus basalis magnocellularis; pvn: para-ventricular nucleus; sn(pr): substantia nigra (pars reticulata); str: striatum; vta: ventral tegmental area.

Biol. Pharm. Bull. **31**(12) 2163—2181 (2008)

H_3 dans le SNC

Table 4. Potential Indications and State of Development of H_3R Antagonists in Clinical Studies

Name	Data results	
	Potential indication	Status
ABT-834	Cognitive impairment	Phase I (Alzheimer's disease)
GSK189254	Narcolepsy	Phase I (dementia)
	Cognitive impairment	Phase I (hyperalgesia *vs.* duloxetine)
	Neuropathic pain	Phase II (narcolepsy)
GSK239512	Cognitive impairment	Phase I (dementia)
		Phase I (PET imaging)
		Phase II (Alzheimer's disease)
GSK835726	Allergy	Phase I (allergic rhinitis)
GSK1004723	Allergy	Phase I (allergic rhinitis)
GW-784568X	Allergy	Phase I/II (allergic rhinitis)
JNJ-17216498	Narcolepsy	Phase II (narcolepsy)
MK0249	Narcolepsy	Phase II (EDS in patients with OSA/HS)
	Cognitive impairment	Phase IIa (cognitive impairment in schizophrenia)
		Phase II (Alzheimer's disease)
		Phase II (ADHD)
PF-03654746	Cognitive impairment	Phase I (PET imaging)
	Allergy	Phase II (ADHD)
		Phase II (allergic rhinitis)
Tiprolisant (BF2.649)	Narcolepsy	Phase II (narcolepsy)
	Epilepsy	Phase II (epilepsy)
	Parkinson's disease	Phase II (sleepiness in Parkinson's disease)
	Schizophrenia	Phase II (cognitive impairment)
	Cognitive impairment	

Biol. Pharm. Bull. **31**(12) 2163—2181 (2008)

Les effets immunomodulateurs médiés par H4

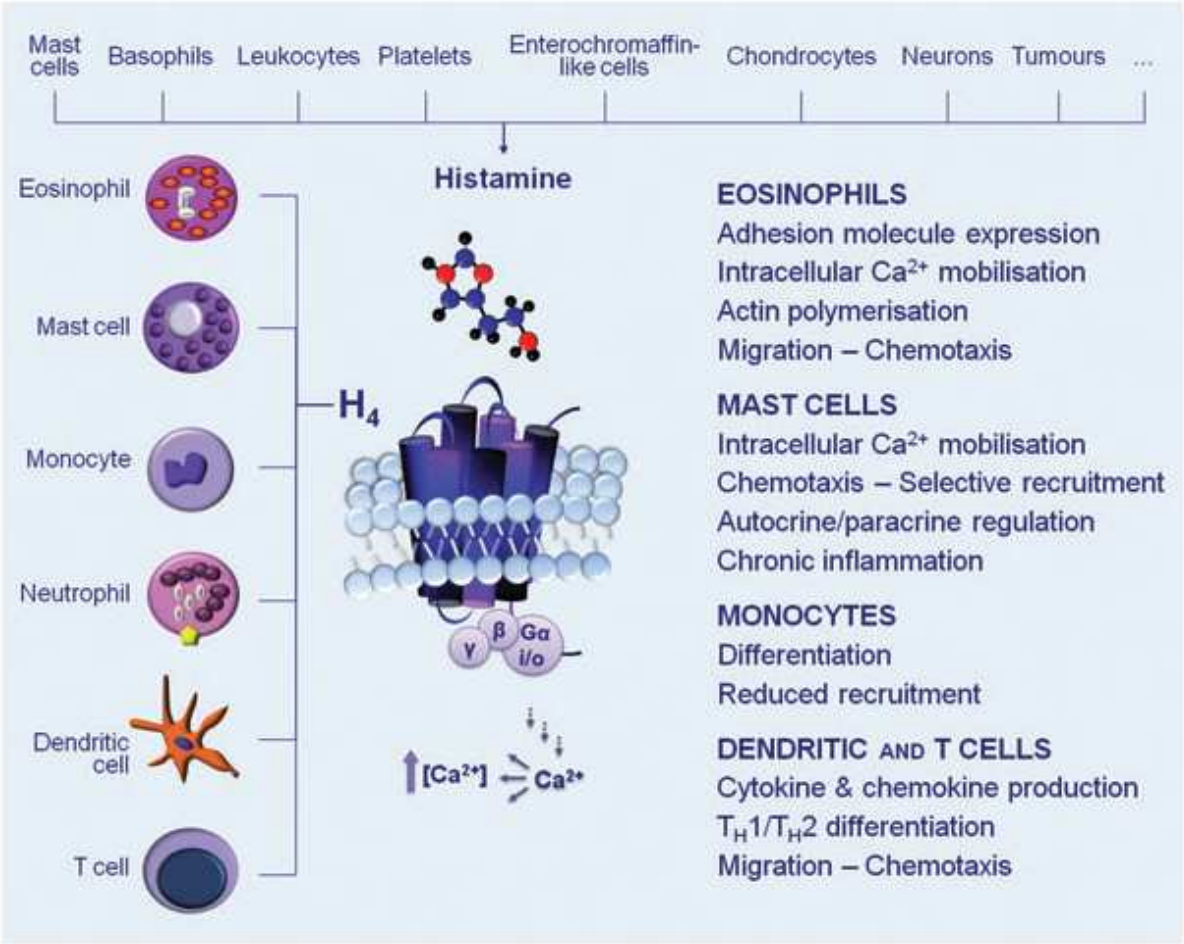


Figure 2 Indicative immunomodulatory actions of histamine that are mediated through histamine H_4 receptors (H_4) predominately expressed in immune cells. $G\alpha_{i/o}$, G-protein; T_H, helper T cell.

British Journal of Pharmacology (2009), 157, 24–33
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0007-1188/09
www.brjpharmacol.org

Pharmacothérapie de l'allergie

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision

Conclusion: These are the most recent and currently the most systematically and transparently developed recommendations about the treatment of allergic rhinitis in adults and children. Patients, clinicians, and policy makers are encouraged to use these recommendations in their daily practice and to support their decisions. (J Allergy Clin Immunol 2010;126:466-76.)

→ Mesures préventives
→ Mesures pharmacologiques

Methodes

TABLE II. A summary of the GRADE approach to grading the quality of evidence for each outcome (see Online Repository 1 for details)

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency	1. Large effect 2. Dose-response	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕◯)
Observational studies	Low	3. Indirectness 4. Imprecision 5. Publication bias	3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	Low (⊕⊕◯◯) Very low (⊕◯◯◯)

TABLE I. Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation ***	Conditional (weak) recommendation *
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

*Guideline panels applying GRADE use the term "conditional" and "weak" synonymously.

Allergies

Rhinoconjonctivites
→ 55% des consultations chez l'allergologue

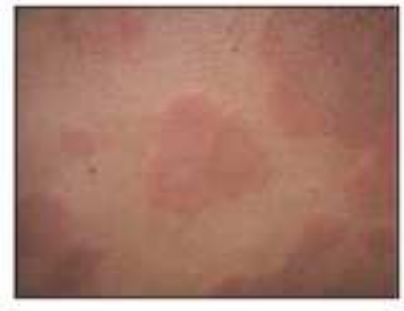
Une proportion élevée de patients qui souffrent de rhinite souffrent également de conjonctivite +/- importante

Rhinites → *Conjonctivites*

Une proportion élevée de patients qui souffrent d'asthme allergique souffrent également de rhinite

Asthmes

Réactions cutanées



Type I (IgE dépendante)

www.ssmg.be/new/files/GJ_textes/2010_Namur_Dezfoulian.pdf

L'application locale d'antihistaminiques est déconseillée car il existe un risque de photosensibilisation et d'hypersensibilité

Allergies : les causes

Pollen → allergies saisonnières
Bouleau, graminées, …

Piqures d'insectes (guèpes, …)

Aliments (arachides, kiwi, fraises, protéines de lait, …)
→ attention certains aliments sont riches en histamine (chocolat, crustacés)
→ attention aux allergies croisées!

Latex

Animaux (poils et protéines de l'urine, …)

Certains polluants peuvent aggraver des profils allergiques.

Mesures préventives en cas d'allergie

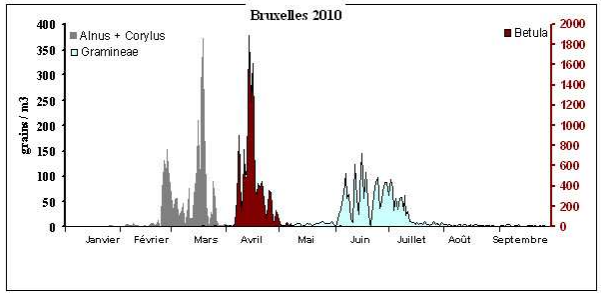
Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision

- Recommander l'allaitement maternel exclusif jusque l'age de 3 mois quel que soit le terrain familial *
- Les mères enceintes ou allaitantes ne doivent pas avoir un régime d'exclusion préventif *
- Les jeunes enfants doivent éviter l'exposition aux acariens et poussières de maison *
- Il n'y a pas lieu déviter l'exposition à des animaux domestiques chez le jeune enfant qui ne présente pas de réactions allergiques *

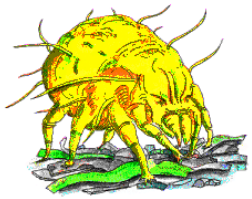
Chez la personne allergique : la prévention constitue le meilleure traitement

- *régime exclusif*
- *mesures préventives importantes pour éliminer les acariens et poussières*
- *mesures préventives pour éviter l'exposition aux pollens*
- *mesures préventives pour éviter l'exposition aux animaux*

Mesures préventives en cas d'allergie



http://airallergy.iph.fgov.be/sites/airallergy/fr/default.aspx



1) logement : pendant la période de chauffage il est recommandé une humidité de l'air relative ne dépassant pas 50 % et une température de l'air de 16 °C -18°C dans la chambre à coucher et de 19 -21°C dans le salon. Aérer régulièrement les chambres surtout en cas de temps sec ou froid. Eviter les plantes vertes et les animaux domestiques. Exclure les animaux des chambres à coucher.

2) Lit : Utiliser des protège-matelas imperméables aux acariens. Pour le coussin et le duvet utiliser des housses imperméables aux acariens ou laver régulièrement les coussins et duvets lavables à 60°C et bien les sècher.

3) Nettoyage : Dépoussiérage une fois par semaine avec un chiffon légèrement humide. Eloigner les éléments susceptibles d'accumuler la poussière (tapis muraux, rideaux lourds, animaux en peluche non lavables). Préférer les sols lavables à l'eau (parquet, linoléum, dallage), eviter les décors qui ont tendances à accumuler la poussière.

4) Vacances : A cause d'un air sec et froid, il est rare de trouver des acariens dans des lieux situés a plus de 1200 m d'altitude. Les vacances en montagne sont donc recommandées.

Traitements pharmacologiques de la rhinite allergique

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision

• En cas de rhinites allergiques, **les anti-histamines de nouvelle génération**, par voie orale sont recommandés **

• Chez le jeune enfant qui présente une dermatite atopique et/ou un risque familial de développer de l'asthme, **les anti-histamines par voie orale ne sont pas recommandés pour prévenir l'asthme** *

• Chez l'adulte et l'enfant les anti-histamines administrés par **voie nasale** peuvent être utilisés en cas de **rhinite allergique saisonnière**, en cas de rhinite chronique, ils ne sont pas recommandés *

• Chez l'adulte et l'enfant présentant une rhinite allergique saisonnière ou chronique, les anti-histamines de 1ère génération administrés par **voie orale** sont à préférer aux antihistaminiques adminitrés par **voie nasale**

• Chez l'adulte et l'enfant présentant une rhinite allergique saisonnière ou chronique, les glucocorticoides par voie nasales sont probablement plus efficaces que les antihistaminiques ou les antagonistes des leucotriènes adminitrés par **voie orale.** En cas de refus de la voie nasale, l'alternative est acceptable.

•Chez l'adulte, l'enfant et le jeune enfant, les antagonistes des leucotriènes peuvent être utilisés en cas de rhinite saisonnière (peu d'efficacité dans la rhinite chronique), les antihistaminiques sont à préférer (cout)

Traitements pharmacologiques de la rhinite allergique

• Pour la rhinite allergique saisonnière, dans la mesure du possible, **éviter les décongestionnants** (per os ou voie nasale) ou en limiter l'utilisation à de courts traitements.

• Pour la rhinite allergique chronique, les décongestionnants ne sont pas recommandés

• ëtre attentifs aux signes d'une infection (otites, sinusites, asthme)

→ renvoyer chez le médecin

Traitements pharmacologiques

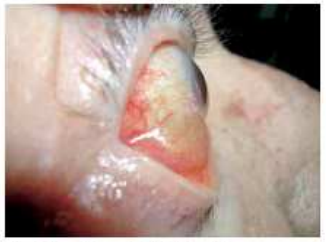


Figure 1. Acute allergic conjunctivitis (chelmosis).

Figure 2. Allergic conjunctivitis.

Conjonctivites allergiques:

Démangeaisons, rougeurs
Larmoiement, gonflement

En usage local

→cromoglycate de sodium (prévient la libérations des médiateurs) (4X /j; prophyllaxie)

→ Antihistaminiques (△ glaucome, irritation, effet rebound)
→ AINS
→ Glucocorticoides

→Application de linges frais (et propres!!!)
→Utilisation de larmes artificielles

Conseils généraux lors de la dispensation d'antihistaminiques

- Vérifier l'age du patient
  - enfant en dessous de 3 ans
  - Adaptation posologique
- Conseils de prise :
  - Souvent 1 X le soir
- Surtout si utilisation d'un anti H1 de première génération:
  - Prévenir du risque de sédation
  - Etre attentifs aux effets indésirables
  - Tenir compte des interactions médicamenteuses/"alimentaires" (alcool)[2]