



# Anaphylaxie et Curares

**Professeur Paul Michel MERTES**

**Service d'anesthésie-réanimation chirurgicale  
Hôpitaux Universitaires de Strasbourg  
Nouvel Hôpital Civil – U961**

***[paul-michel.mertes@chru-strasbourg.fr](mailto:paul-michel.mertes@chru-strasbourg.fr)***

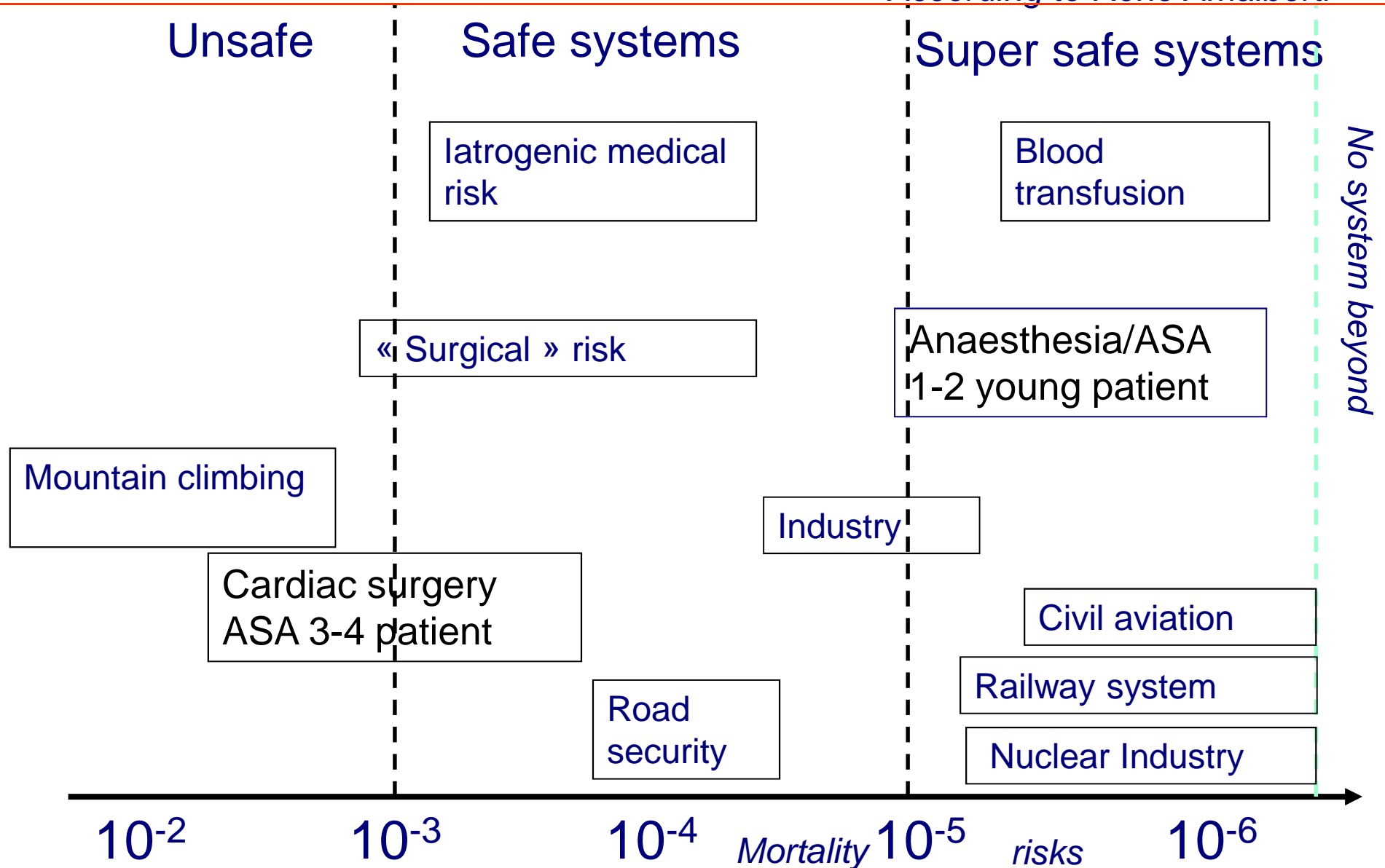


# Conflits d'Intérêts

- Académique:
  - Président du GERAP
  - Investigateur ALPHO

# Risks in medicine compared to other technical fields

According to René Amalberti





# Anesthésie Générale

- Combinaison :

- Hypnotique (sommeil)

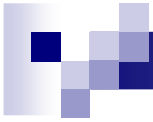
- Morphinique (douleur)

- Curare (intubation, relaxation musculaire)

- ➔ pas d'éviction inutile

- ➔ identification d'association "utilisable" pour les procédures ultérieures

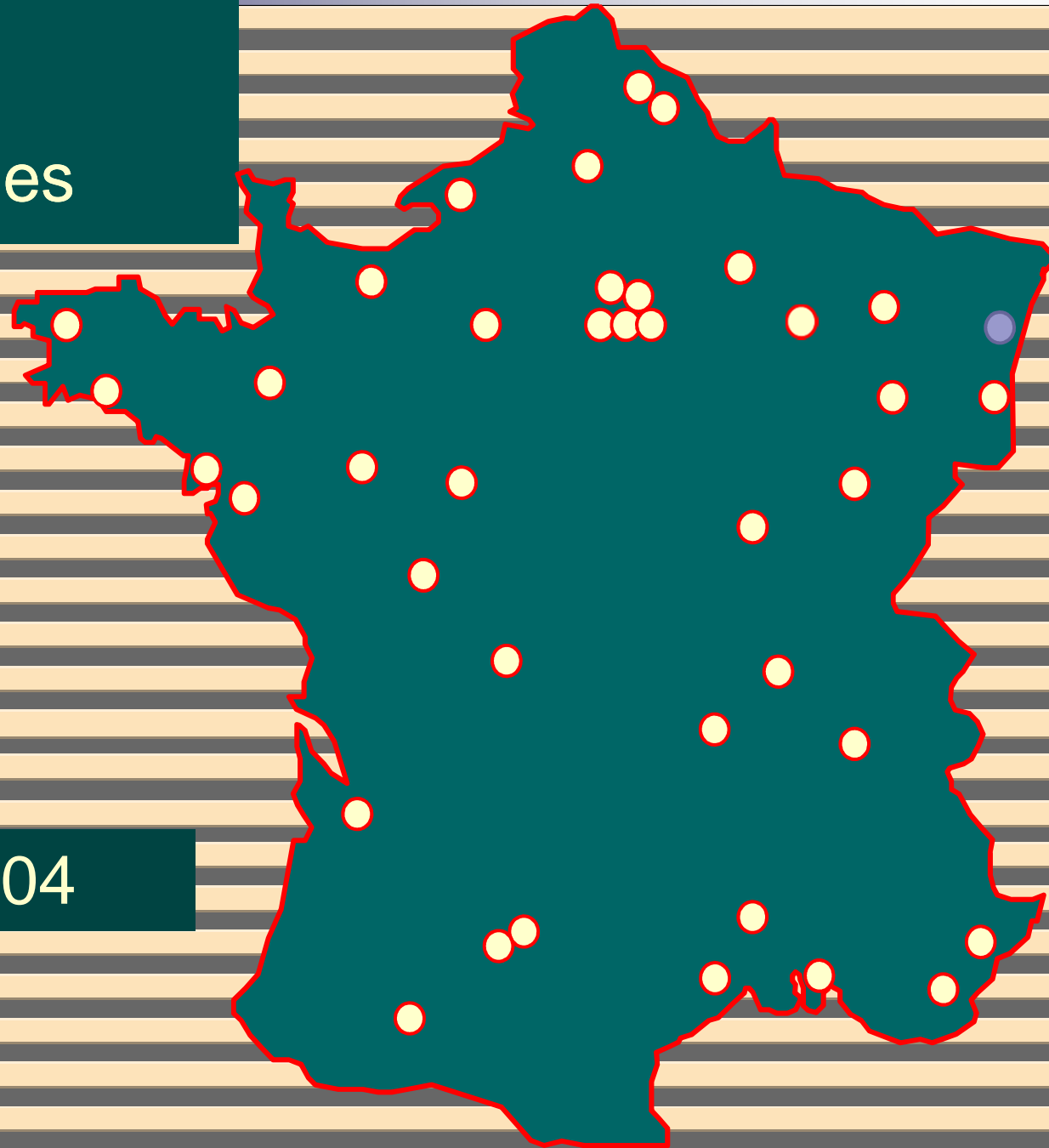
Et de nombreux autres produits: latex, antibiotiques, gélatines, colorants....



# Epidémiologie

**GERAP**  
42 centres  
diagnostiques

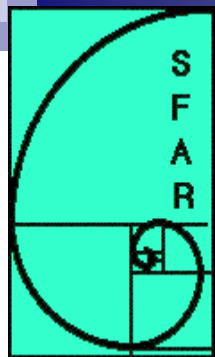
1997-2004





# Patients et méthodes

- 42 centres d'allergo-anesthésie membres du GERAP
- 1er Janvier 1997 au 31 Décembre 2004
- Données comparées aux résultats du réseau de Pharmacovigilance obtenus pour la période 2003-2004
- Nombre de sujets exposés établi grâce à la base de données SFAR-Inserm de 1996
- Incidence des réactions estimée par une méthode de capture/recapture.



# Société Française d'Anesthésie Réanimation

Recommandations pratiques cliniques 2001  
Révision 2011

« *Réduction du risque de  
l'anaphylaxie pendant l'anesthésie* »

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Référence : [www.sfar.org/allergiefr.html](http://www.sfar.org/allergiefr.html)





# Diagnostic

## Recommandations SFAR

- Au moment de la réaction
  - Tryptase plasmatique, Histamine plasmatique
    - T1 : dans les 30 minutes qui suivent la réaction anaphylactique
    - T2 : 1 à 2 heures après la réaction anaphylactique.  
*Histamine : tube EDTA ; Tryptase: tube EDTA ou tube sec*
  - IgE Ammoniums Quaternaires, latex, (AB, thiopental, ...)
- Après la réaction
  - Tryptase plasmatique
    - T3 : plus de 24 heures après la réaction anaphylactique.
  - **Bilan allergologique 6 semaines après la réaction**
- En pratique
  - Pas de bilan tardif / les décès
  - Négligence de certains patients...pas de bilan allergo



# Bilan allergologique

- En milieu hospitalier (réseau GERAP)
- Pas d'AH1 depuis 8 jours
- Témoins + et -
- Prick-tests, IDR avec curares dilués
- Recommandations/dilutions

	Prick-tests	IDR
ATRACURIUM	1 mg/ml	0,001 mg/ml
CISATRACURIUM	2 mg/ml	0,002 à 0,2 mg/ml
MIVACURIUM	0,2 mg/ml	0,2 mg/ml
ROCURONIUM	10 mg/ml	0,01 à 0,1 mg/ml
SUXAMETHONIUM	10 mg/ml	0,01 à 0,1 mg/ml
VECURONIUM	4 mg/ml	0,4 à 0,004 mg/ml



# Patients

1er Janvier 1997 – 31 Décembre 2004

**2516 patients**

Non IgE-médiée

700 (27,82 %)

IgE-médiée

1816 (72,18 %)



## Patients

- **Femme : n = 1760 (69,95 %)**
- **Homme : n = 756 (30,5 %)**

Substances incriminées dans les réactions IgE-dépendantes  
 durant l'anesthésie (1816 patients, 1851 substances)  
 entre le 1er janvier 1997 et le 31 décembre 2004 en France

Substances incriminés	%	Nombre de patients
<b>Curares</b> ( <i>n = 1067, 58,08 %</i> )	Succinylcholine	33,40
	Rocuronium	29,30
	Atracurium	19,30
	Vécuronium	10,20
	Pancuronium	3,60
	Mivacurium	2,50
	Cisatracurium	1,70
<hr/>		
<b>Latex</b> ( <i>n = 361, 19,65 %</i> )		
<b>Antibiotiques</b> ( <i>n = 236, 12,85 %</i> )	Pénicillines	115
	Céphalosporines	88
	Autres	33
<hr/>		
<b>Hypnotiques</b> ( <i>n = 43, 2,34 %</i> )	Propofol	55,80
	Midazolam	32,60
	Pentothal	9,30
	Kétamine	2,30

Substances incriminées dans les réactions IgE-dépendantes durant l'anesthésie (1816 patients, 1851 substances) entre le 1<sup>er</sup> janvier 1997 et le 31 décembre 2004 en France

Substances incriminés		%	Nombre de patients
<b>Morphiniques</b> ( <i>n</i> = 31, 1,69 %)	Morphine	35,5	11
	Fentanyl	22,6	7
	Sufentanil	22,6	7
	Nalbuphine	12,9	4
	Rémifentanil	6,5	2
<b>Colloïdes</b> ( <i>n</i> = 63, 3,43 %)	Gélatines	88,9	56
	Amidons	9,5	6
	Albumine	1,6	1
<b>Anesthésiques locaux</b> ( <i>n</i> = 6, 0,33 %)	Bupivacaïne	50,0	3
	Lidocaïne	33,3	2
	Mépipivacaïne	16,7	1
<b>Autres</b> ( <i>n</i> = 44, 2,40 %)	Colorants	27,3	12
	Propacétamol	20,5	9
	Aprotinine	11,5	5
	Protéine	9,1	4
	Divers	31,6	14

Drugs responsible for HSI-IgE perianesthetic reactions  
(8 epidemiologic surveys of GERAP)

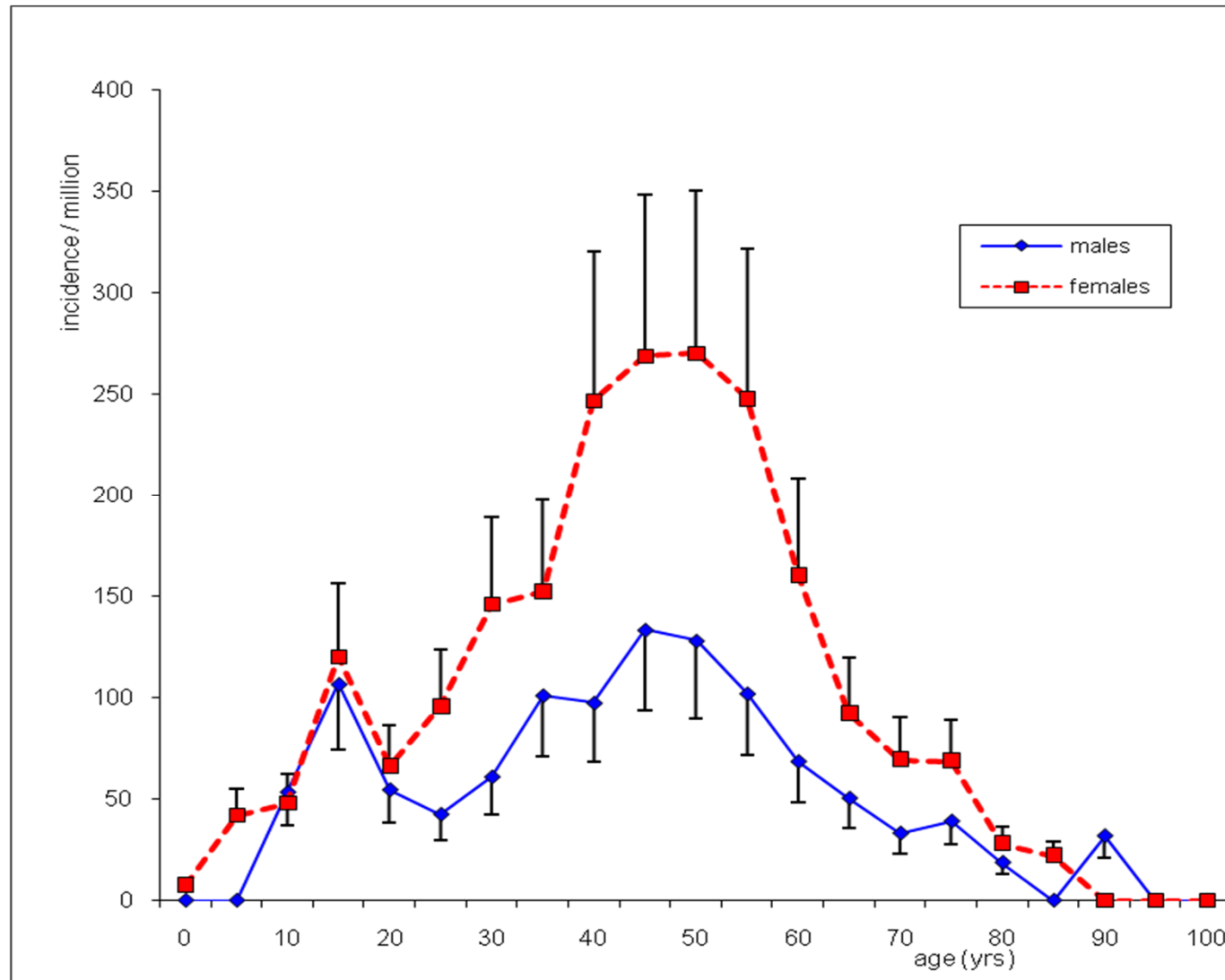
	1989 *	1992 *	1994 *	1996 *	1998 **	2000 *	2002 *	2004	2006
	<i>n</i> =821	<i>n</i> =813	<i>n</i> =1030	<i>n</i> =734	<i>n</i> =486	<i>n</i> =518	<i>n</i> =502	<i>n</i> =406	<i>n</i> =602
<b>NMBAs</b>	81,0	70,2	59,2	61,6	69,2	58,2	54,0	49,6	48
<b>Latex</b>	0,5	12,5	19,0	16,6	12,1	16,7	22,3	26,4	20,3
<b>Hypnotics</b>	11,0	5,6	8,0	5,1	3,7	3,4	0,8	1,4	0,8
<b>Opioids</b>	3,0	1,7	3,5	2,7	1,4	1,3	2,4	1,4	1,8
<b>Colloids</b>	0,5	4,6	5,0	3,1	2,7	4,0	2,8	4,6	2,3
<b>Antib</b>	2,0	2,6	3,1	8,3	8,0	15,1	14,7	12,2	17,9
<b>Others</b>	2,0	2,8	8,3	2,6	2,9	1,3	3,0	4,4	7,1

\* AFAR 1990-1994-1996-1999-2004

\*\* BJA 2001

\*\*\* Anesthesiology 2003

## Incidence annuelle estimée des réactions d'hypersensibilité immédiates IgE-dépendantes selon le sexe et l'âge





## Estimated annual incidence of IgE-mediated allergic reactions during anesthesia

Causal agents	Estimated annual number of case	Estimated annual incidence in France (/million)		
		Male	Overall	Female
<b>Overall</b>	780 [555-1005]		<b>100.6 [76.2-125.3]</b>	
		55.4 [42.0-69.0]		154.9 [117.2-193.1]
<b>NMBAs</b>	458 [326-590]		<b>184.0 [139.3-229.7]</b>	<b>250.9 [189.8-312.9]</b>
		105.5 [79.7-132.0]		
<b>Latex</b>	155 [110-200]		<b>59.1 [44.8-73.6]</b>	
		32.6 [24.7-40.5]		91.0 [68.9-113.4]
<b>Antibiotics</b>	101 [72-131]		-	
<b>Others agents</b>	80 [57-103]		-	

History of atopy, asthma, drug intolerance and food intolerance in patients with immediate IgE-mediated hypersensitivity reactions to neuromuscular blocking agents (NMBAs), latex or antibiotics between January 1, 1997 and December 31, 2004 in France

	<b>Atopy</b>	<b>Asthma</b>	<b>Drug intolerance</b>	<b>Food intolerance</b>
	<b>p &lt; 0.001</b>	<b>p &lt; 0.0001</b>	<b>p &lt; 0.0138</b>	<b>p &lt; 0.0001</b>
<i><b>Neuromuscular blocking agents (NMBAs)</b></i>	<b>15.276</b>	<b>7.123</b>	<b>17.901</b>	<b>3.148</b>
<i><b>Latex</b></i>	<b>30.836</b>	<b>16.715</b>	<b>14.409</b>	<b>21.902</b>
<i><b>Antibiotics</b></i>	<b>14.035</b>	<b>8.333</b>	<b>24.123</b>	<b>0.439</b>

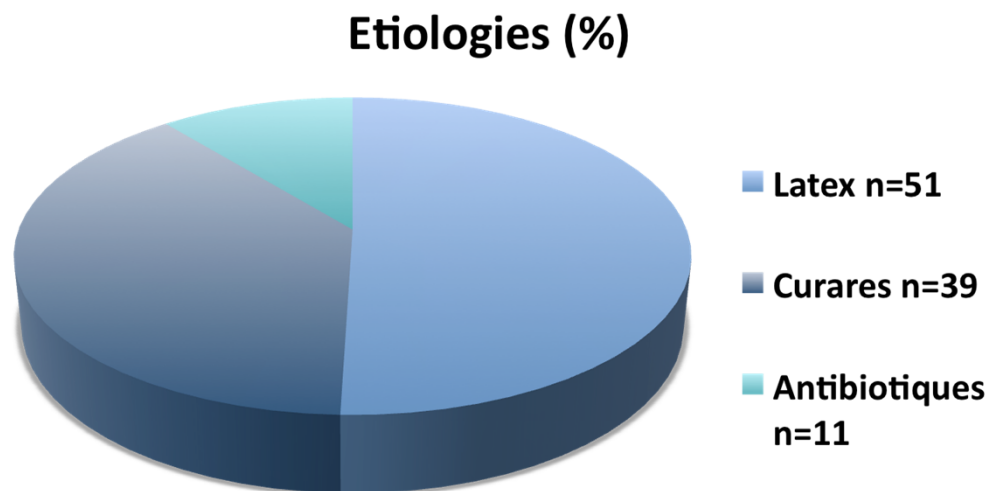


# **Particularités chez l'enfant**

# Résultats

- 266 enfants  
1<sup>er</sup> janvier 1997 – 31 décembre 2004

- 122 réactions IgE-  
médiées : 45,9 %



	Filles	Garçons	p
IgE- médiées	n = 61	n = 61	ns
Non IgE- médiées	n = 66	n = 78	ns

→ Sex-ratio : 1



## *mécanismes physiopathologiques*

- Hypothèses pour expliquer la sensibilisation aux curares et l'augmentation de l'anaphylaxie féminine:
  - L'exposition aux facteurs environnementaux : ammoniums quaternaires des produits cosmétiques
  - Le rôle des facteurs endocriniens



## *hypersensibilité immédiate et sexe féminin*

La prédominance des réactions chez la femme pourrait être expliquée par:

- Le rôle des œstrogènes dans la différenciation lymphocytaire vers un profil TH2

*Chen W. et al. Allergy. 2008, 63 : 1418-27*

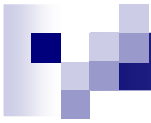
- Le rôle des œstrogènes dans l'activation mastocytaire

*Uemura Y. et al. Hum. Immunol. 2008, 69 : 149-57*



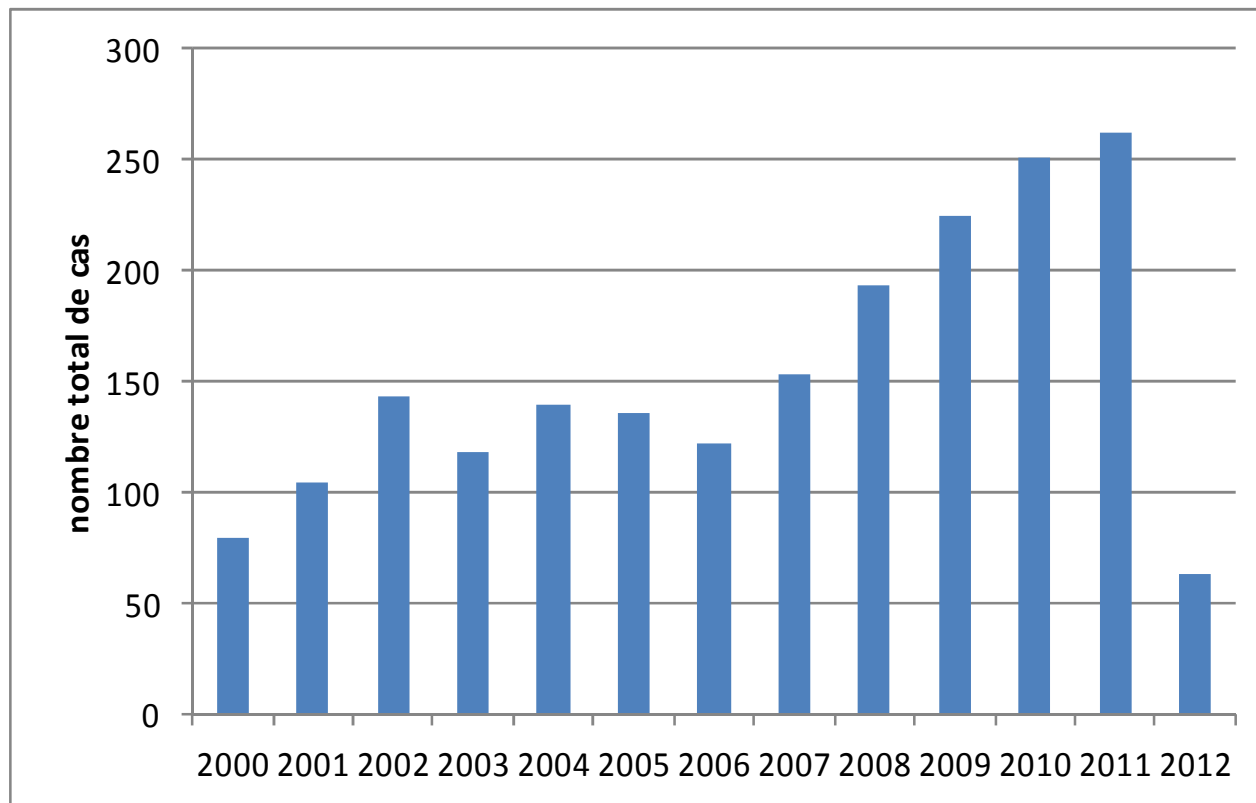
# Signaux récents de PV

- Enquête en 2010 liée à la pholcodine
  - Comparaison des périodes 2003/2004 et 2008/2009
  - Augmentation entre les 2 périodes
- Septembre 2011: augmentation des cas liés à la CELOCURINE/ CRPV de Brest
- Janvier 2012: plusieurs cas successifs avec la CELOCURINE à Paris (Hôpital Lariboisière/CRPV Fernand Widal)
- → Enquête nationale de PV sur tous les curares



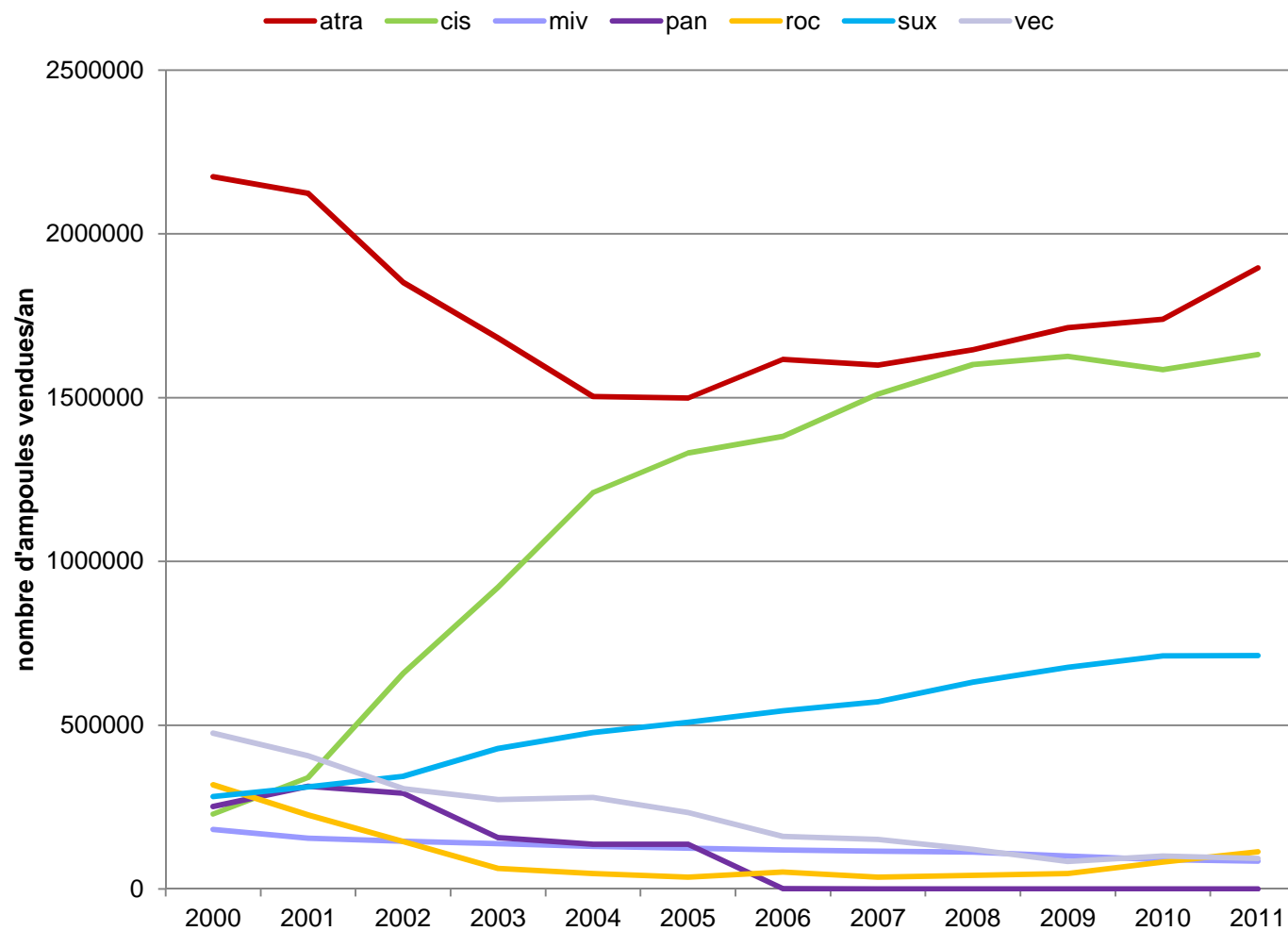
# Données de pharmacovigilance en France entre 2000 et 2011 (juillet 2012)

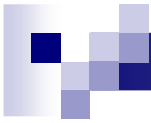
Tous curares





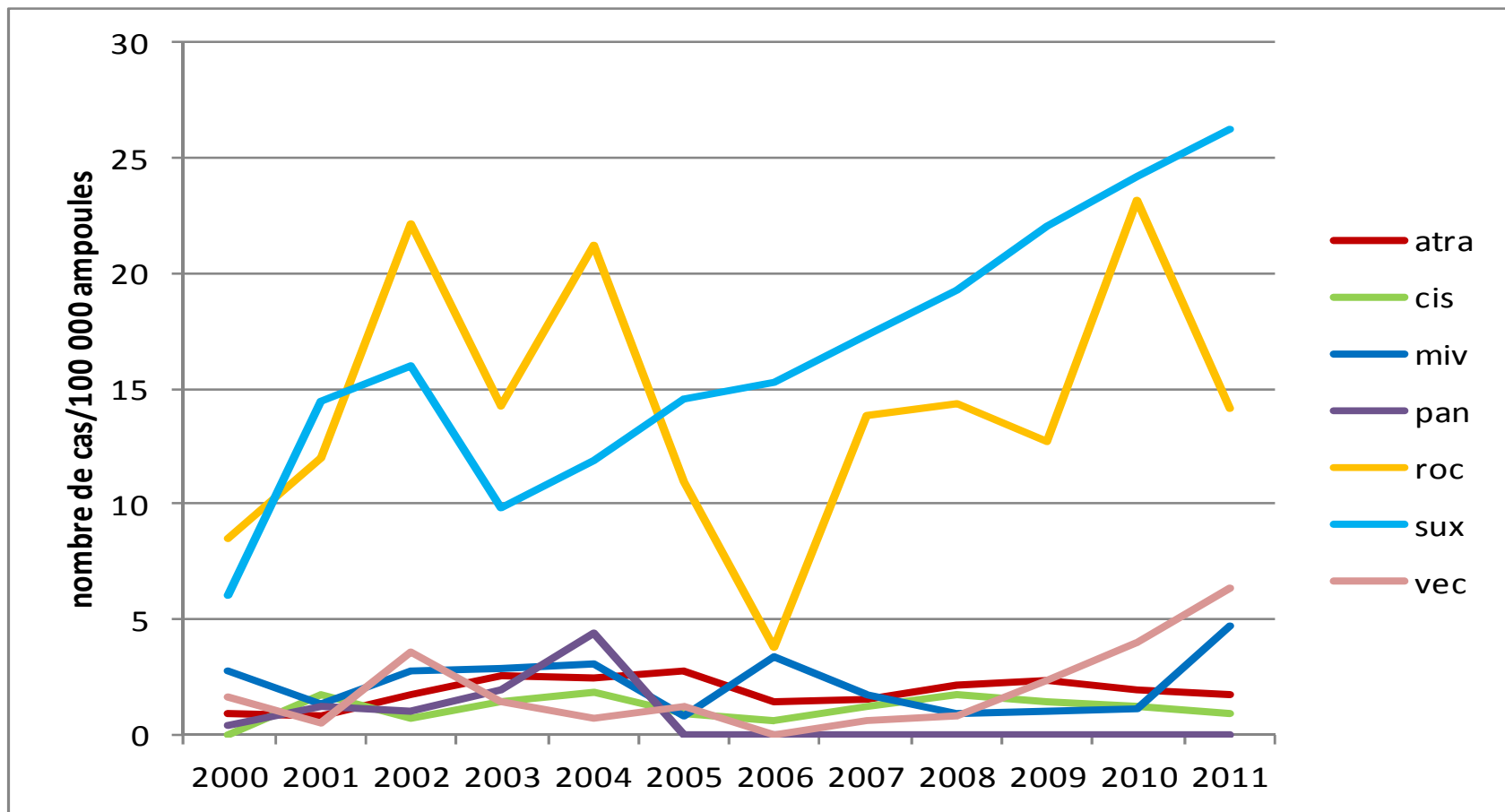
# Ventes annuelles de curares de 2000 à 2011



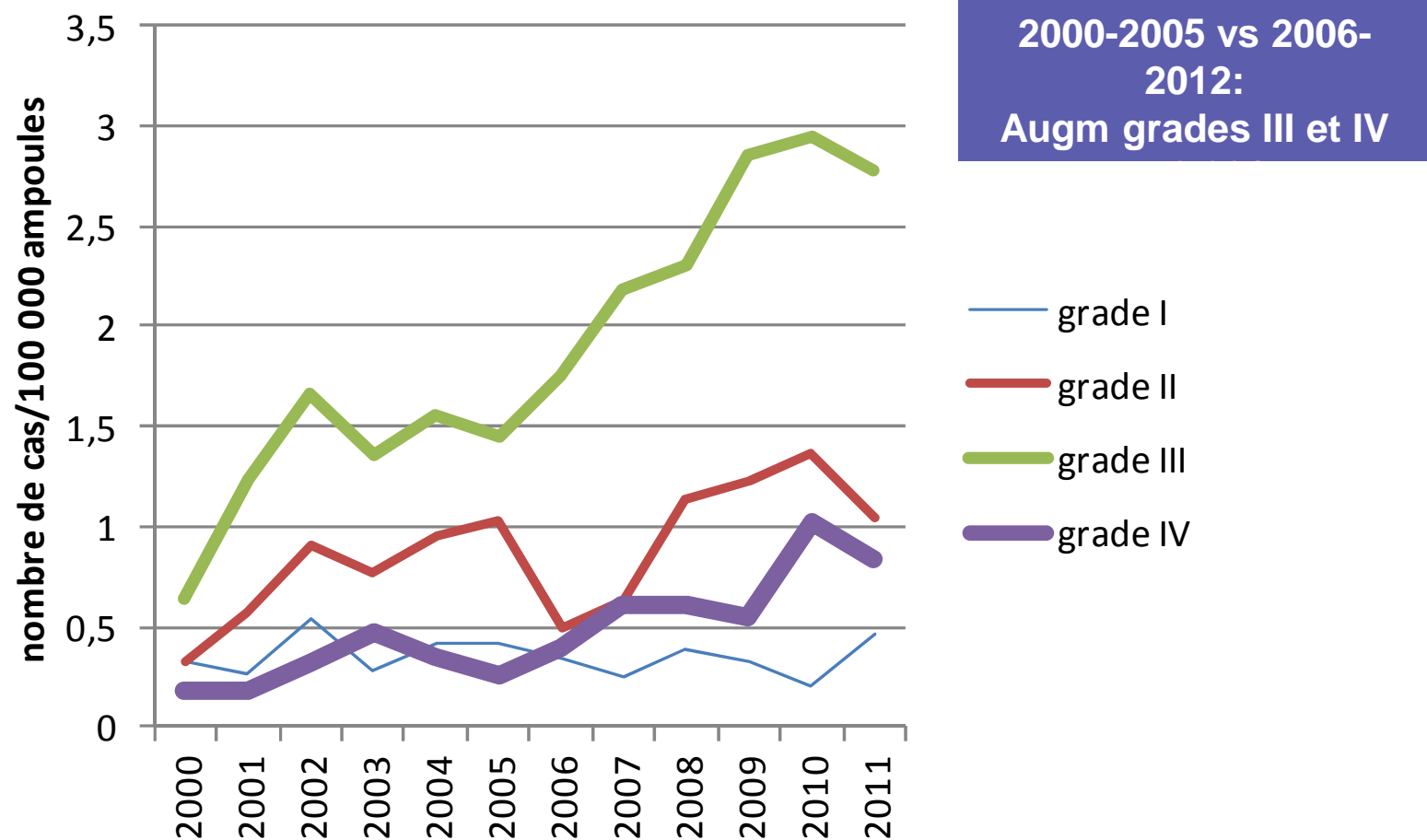


# Données de pharmacovigilance en France

Taux de notification: nb cas/100 000 ampoules vendues



# Augmentation de la sévérité



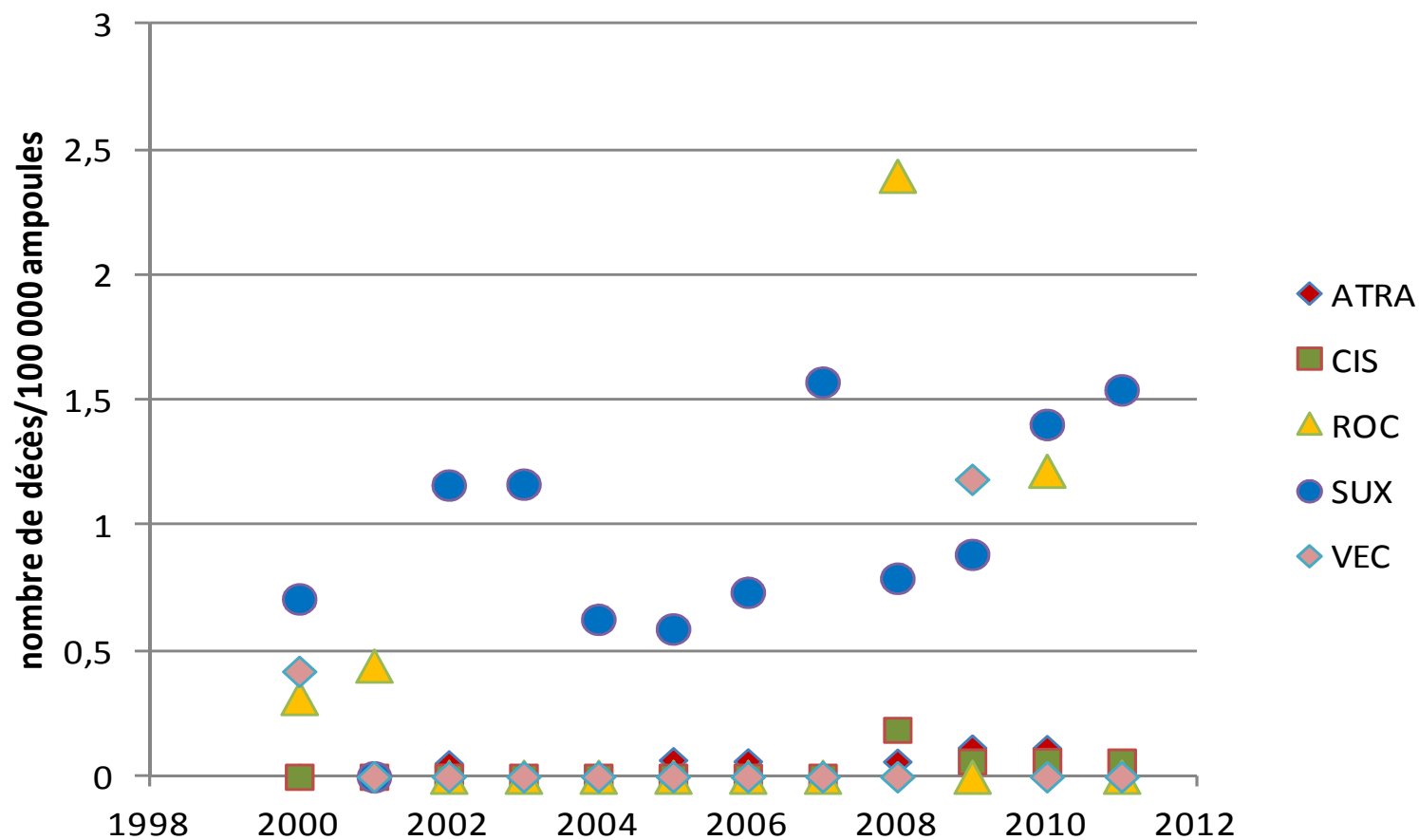


# Décès

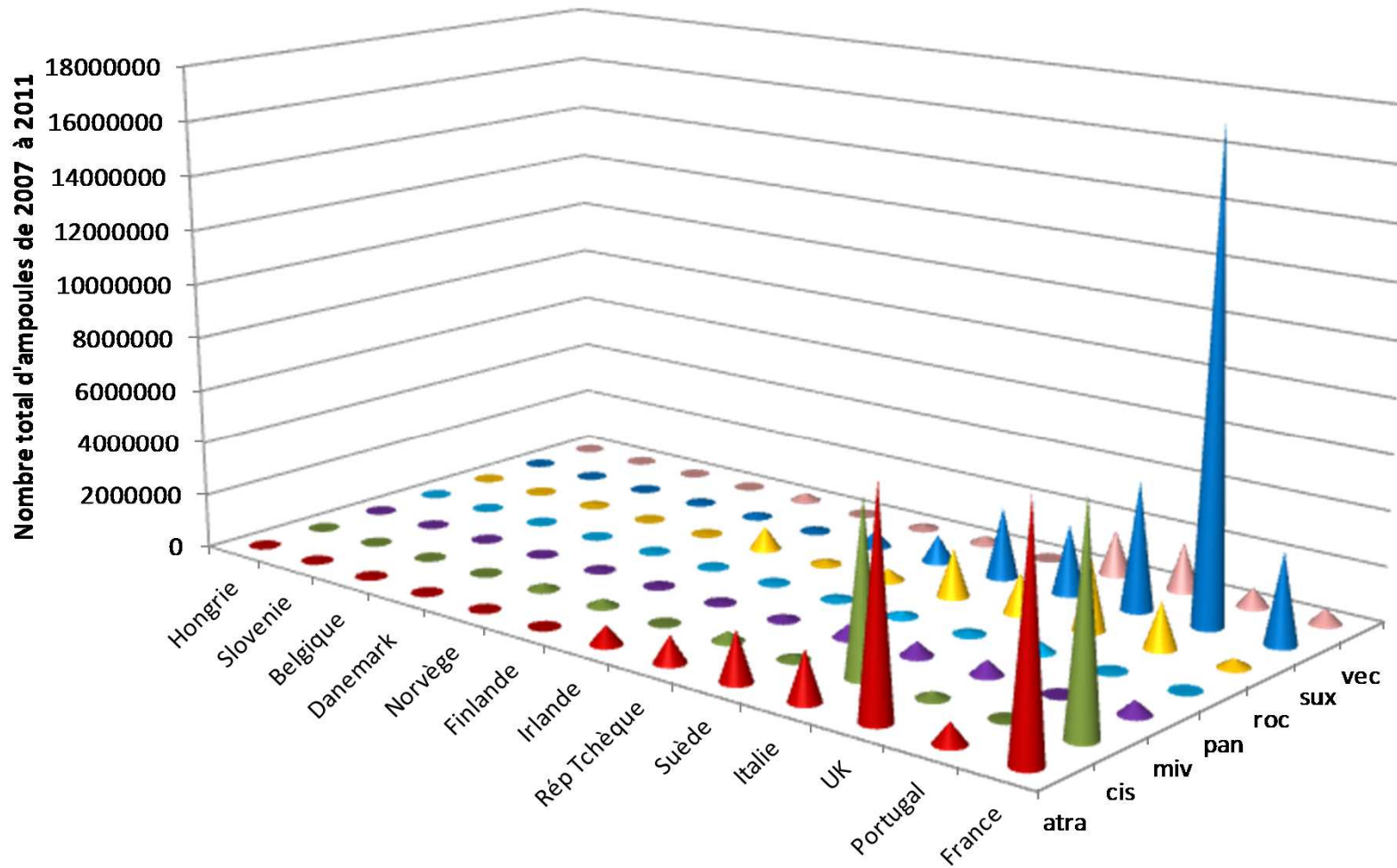
- Données de pharmacovigilance (France)
  - 4% des notifications
  - Hommes
  - Femme âgées, femmes obèses (IMC moy =34)
  - Urgence
  - Contexte inflammatoire
  - Suxaméthonium
  - ATCD de RAP
- Autres pays: 3 à 9%
- Mortalité de l'anesthésie: 1 décès pour 145500 (1999)

# Augmentation des décès notifiés

2006-2011 > 2000-2005 (P=0,029)



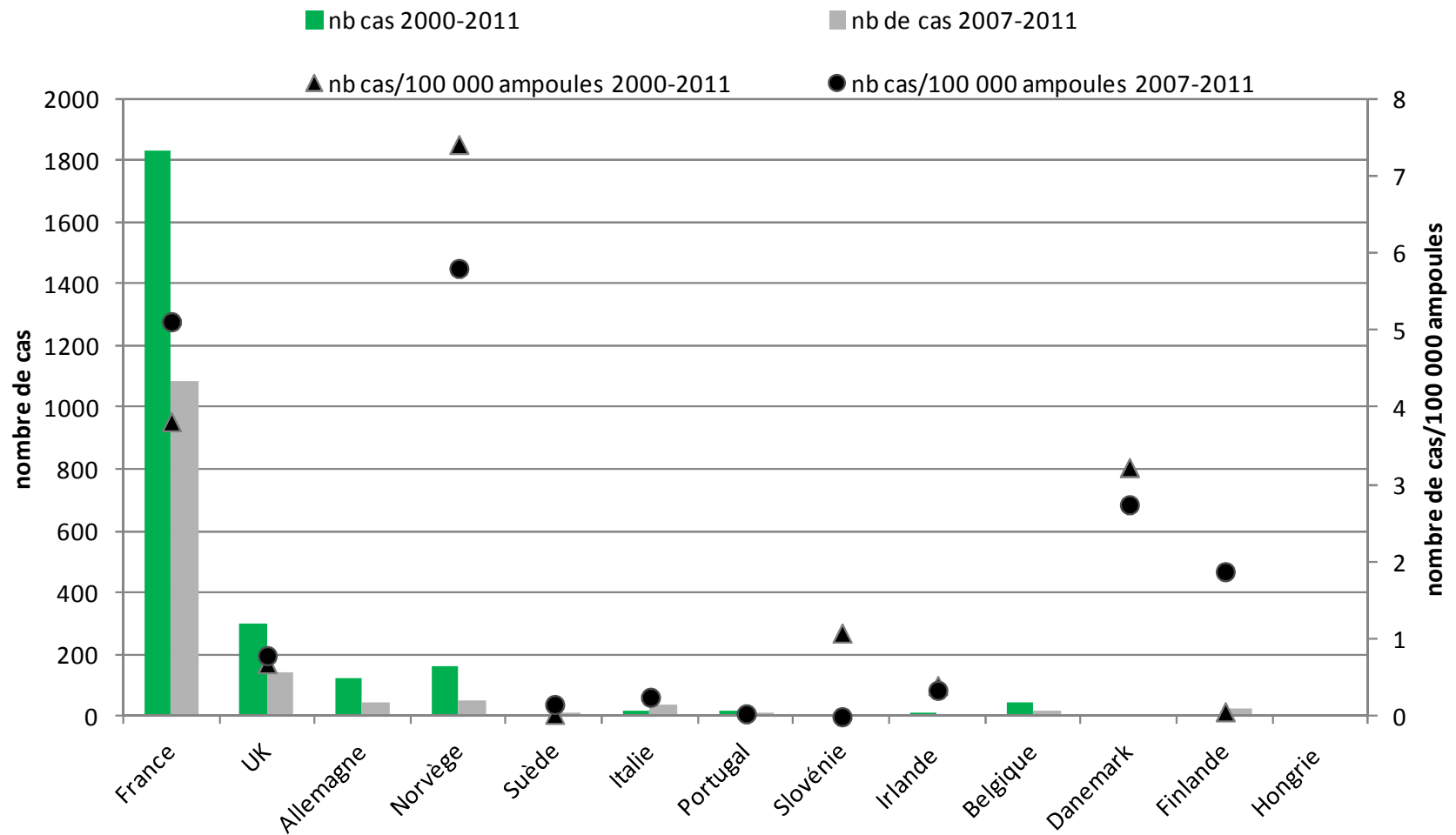
# Répartition des ventes de curares





# Données de pharmacovigilance en Europe

## tous curares









**Existe-t-il une expression  
clinique particulière ?**



# Gravité des réactions

- **Grade I** : présence de signes cutanés.
- **Grade II** : présence de symptômes tels que réaction cutanée, hypotension artérielle (définie par une baisse de 30% associée à une tachycardie inexpliquée), toux ou trouble de la ventilation mécanique, mais **absence de mise en jeu du pronostic vital**.
- **Grade III** : **présence de symptômes mettant en jeu le pronostic vital** tels que collapsus cardiovasculaire, tachycardie, bradycardie, arythmie, bronchospasme sévère.
- **Grade IV** : arrêt circulatoire, arrêt cardiaque ou respiratoire.

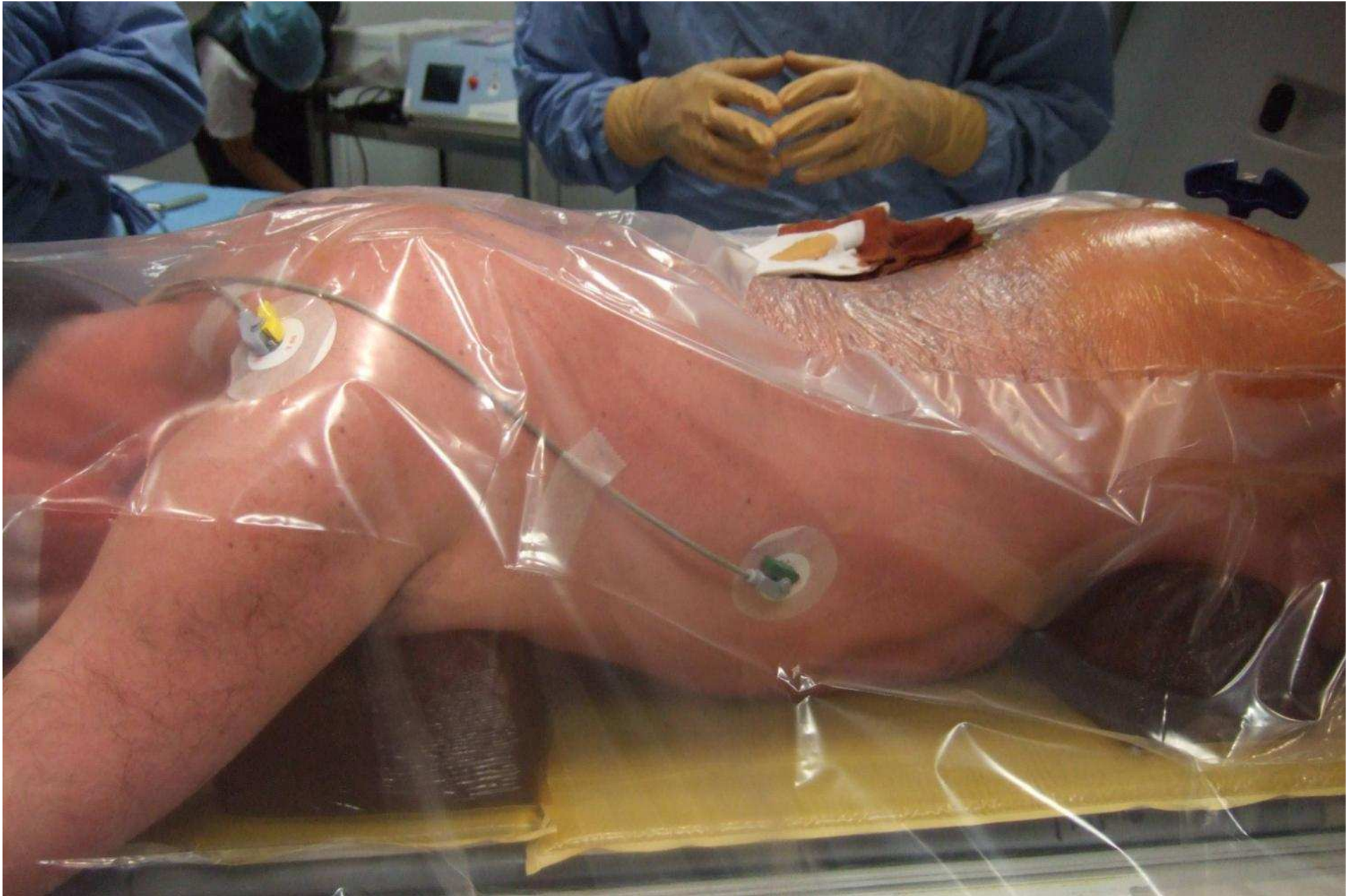
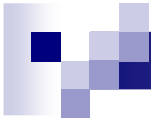


# Manifestations initiales

- ✓ Moment de survenue :
  - dans les minutes suivant l'injection de l'agent responsable

# Position Genupectorale Intervention







# HSI -IgE médiée et moment de survenue

## Pendant l'induction anesthésique

- Curares : réaction sévère dès les premières secondes
- Antibiotiques
- Produits de remplissage
- Désinfectants
- Hypnotiques : rare
- Morphinomimétiques : exceptionnel



# Traitement



# Sugammadex in the management of rocuronium-induced anaphylaxis

- 33 ans, laparoscopie, **rocuronium 0,39 mg/kg**, adrénaline 4 mg, m+19 **sugammadex 6,5 mg/kg**, puis adrénaline 0,65 et metaraminol 1 mg *McDonnell et al, BJA 106 (2): 199–201 (2011)*
- 66 ans, cimentoplastie, **rocuronium 0,6 mg/kg**, grade III, adrénaline 0,2 mg, PA remonte à 75 mmHg, **sugammadex 4 mg/kg** reversion du bloc, PA 100 mmHg. *Motamed et al, JACP 2012*
- 47 ans, cholecystectomie, 78 kg, **rocuronium 50mg**, grade III, adrénaline 0,17 mcg/kg/min, transfert en ICU. Après 1 h, **sugammadex 400mg**, réduction des doses d'adrénaline de moitié. *Funnel et al, BJA, doi:10.1093/bja/aer211*
- 51 ans, hernie ombilicale, 112 kg, **rocuronium 0,45 mg/kg**, grade III, adrénaline 0,5 mg en 15 min, 18 min : adrénaline 0,2 mg et **sugammadex 2000 mg (18 mg/kg)**, amélioration, SE adrénaline 0,5 mg/h sevrée en 60 min. *Raft et al, AFAR 31 (2012) 158–161*
- 62 ans, mastectomie, 45 kg, **Rocuronium 20 mg**, grade II, pas adrénaline, , 30 min : **sugammadex 200mg**, regression erytheme, *Kawano et al., Journal of Clinical Anesthesia (2012) 24, 62–64*

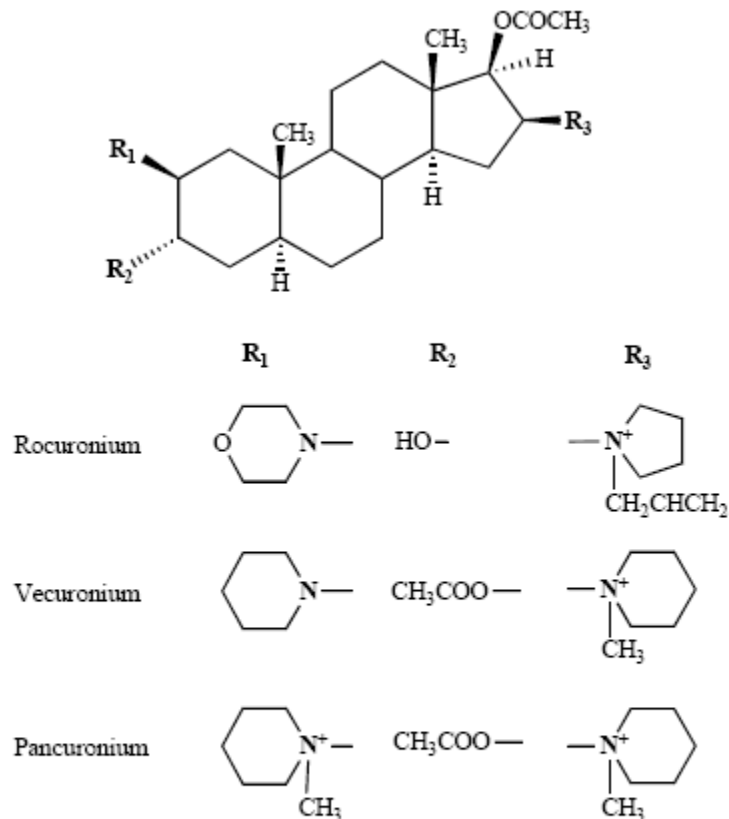




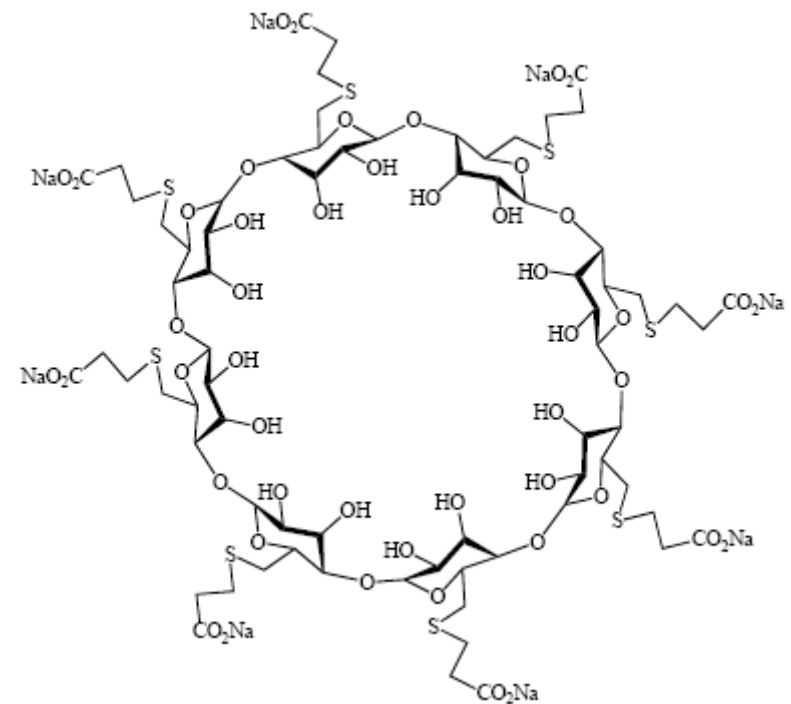
# Sugammadex and rocuronium-induced anaphylaxis

- Anaphylaxis grade III
- Boluses of epinephrine and steroids / 18 min after induction the patient suddenly and dramatically improved.
- Arterial pressure and the heart rate normalized airway pressures decreased rapidly.
- patient was extubated after a further 15 min of normal ventilation.
- Skin tests + rocuronium, cross-reactivity with steroid and benzyliso

# Rocuronium / Sugammadex



**Fig. (2).** Structures of the non-depolarizing and competitive aminosteroid neuromuscular blocking drugs rocuronium, vecuronium and pancuronium. Note the morpholino and pyrrolidinium groups at positions 2 and 16 respectively of rocuronium.



Two-dimensional structure of sugammadex, 6-perdeoxy-6-per(2-carboxyethyl)thio- $\gamma$ -cyclodextrin sodium salt showing the thio(2-carboxyethyl) sodium group linked at position 6 of each of the eight glucopyranose units.

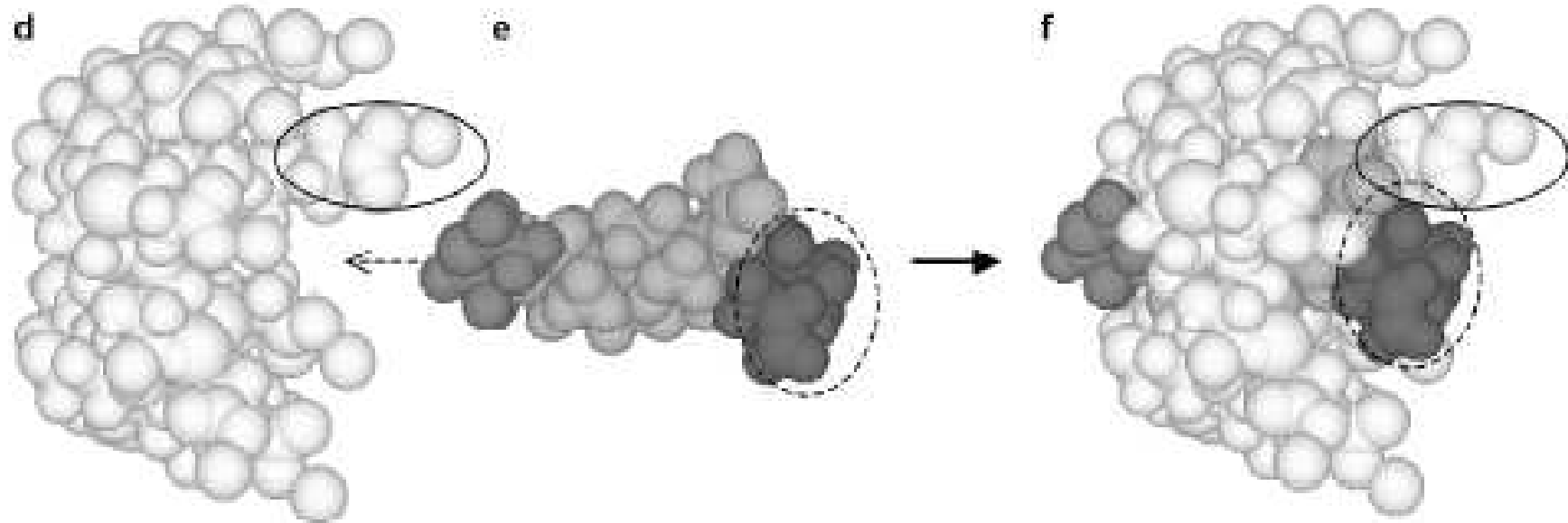


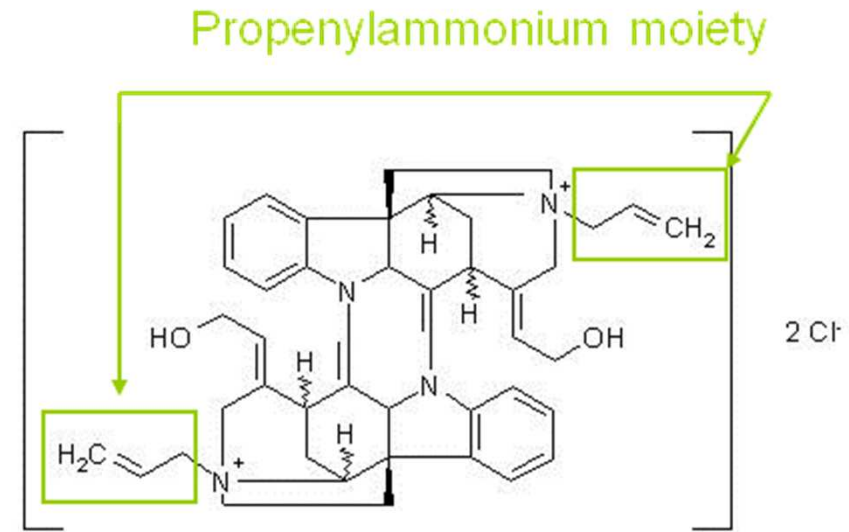
Fig. (6). Space filling ball-and-stick (a,b,c) and CPK (d,e,f) three-dimensional molecular models illustrating the encapsulation of the rocuronium molecule (b and e) by sugammadex (a and d) to form the rocuronium-sugammadex inclusion complex (c and f). The pyrrolidinium quaternary ammonium group (circled) and the tertiary ammonium group, part of the morpholine ring, are shown in dark shading at the right and left hand ends respectively of the rocuronium molecule. In the inclusion complex, the quaternary ammonium group attached to ring D of rocuronium (see Fig. 5) is visible at the primary rim end (right hand side) surrounded by thio(2-carboxyethyl) sodium groups (c,f). One of the eight thio(2-carboxyethyl) sodium groups of sugammadex is ringed. The morpholine group containing the tertiary ring nitrogen and attached at position 2 of the rocuronium molecule protrudes from the complex at the secondary rim end (left hand side). The hydroxyl group at position 3 is behind the morpholine ring in the selected view. All four rings A-D of the rocuronium steroid nucleus and the ~11Å C3 – C16 length are within the sugammadex extended cavity.

Constante d'association:

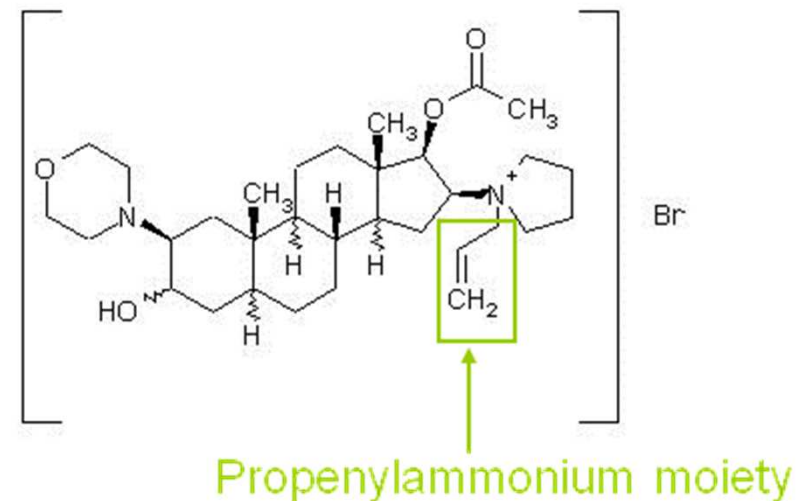
- rocuronium-sugammadex:  $K_a 1,8 \cdot 10^7 M^{-1}$
- rocuronium-IgE:  $K_a 10^{10} 10^{11} M^{-1}?$

# Alcuronium - Rocuronium

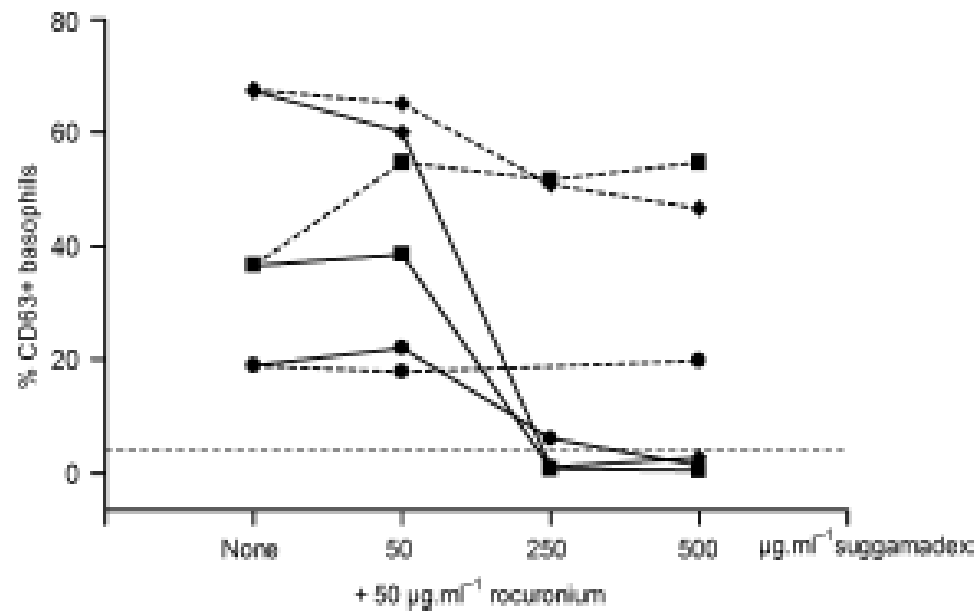
- The propenylammonium moieties of **alcuronium** are chemically unrelated to the substituted ammonium or amine groups on the other NMBAs but it also occurs on rocuronium.



- As for alcuronium in the late 1970s, **rocuronium** has been claimed to be at high risk for anaphylaxis. If this is true, propenylammonium moieties present in both NMBAs may account for the apparent increased allergenicity.

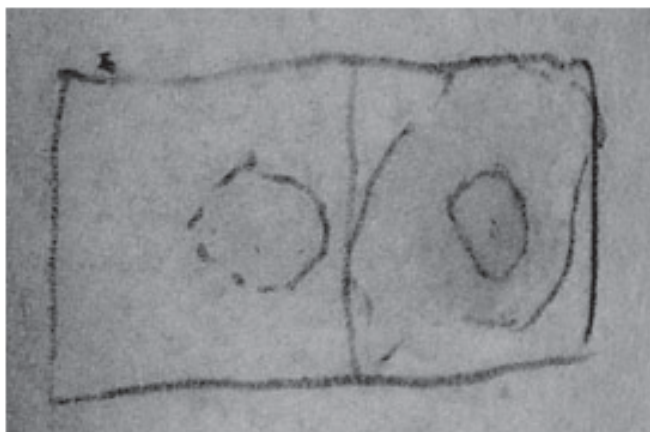


## Rocuronium-induced anaphylaxis is probably not mitigated by sugammadex: evidence from an in vitro experiment



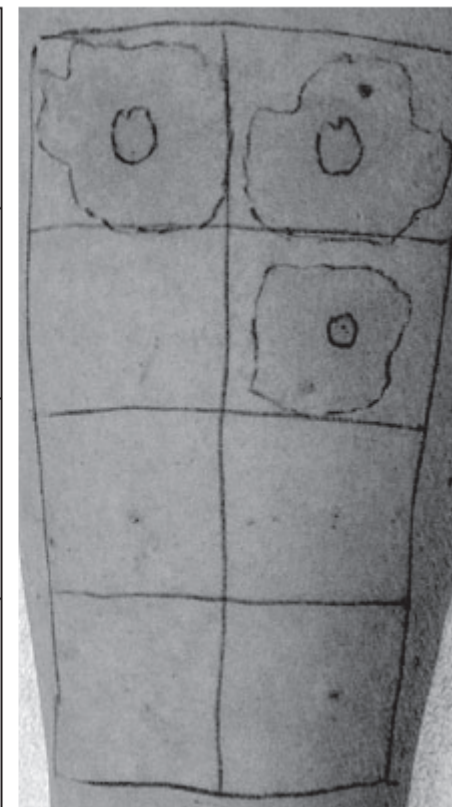
**Figure 2** Dose-dependent inhibition of rocuronium-induced basophil activation in three rocuronium-allergic patients. Solid line: pre-incubated mixture of rocuronium and sugammadex. Dotted line: addition of sugammadex after 3 min of activation with rocuronium.

# The role of sugammadex in the development and modification of an allergic response to rocuronium: evidence from a cutaneous model



<p><b>Sugammadex</b> 0.13 mg.ml<sup>-1</sup> followed by <b>rocuronium</b></p>	<p><b>Rocuronium</b> followed by <b>sugammadex</b> 1.3 mg.ml<sup>-1</sup></p>
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Rocuronium followed by sugammadex 0.13 mg.ml <sup>-1</sup>	Rocuronium 0.01 mg.ml <sup>-1</sup>
Saline 0.9%	Histamine
Low-dose sugammadex (0.13 mg.ml <sup>-1</sup> )	Pre-mixed rocuronium with sugammadex (1:4)
High-dose sugammadex (1.3 mg.ml <sup>-1</sup> )	Pre-mixed rocuronium with sugammadex (1:20)





# Quelle dose de Sugammadex en cas d'allergie?

- Constante d'association:
  - rocuronium-sugammadex:  $K_a 1,8 \cdot 10^7 M^{-1}$
  - rocuronium-IgE:  $K_a 10^{10} 10^{11} M^{-1}$ ?
- Rocuronium 0.4 à 0.6 mg/kg → Sugammadex 4 à 16 mg/kg
- Rocuronium 1.2 mg/kg → Sugammadex ?



# Allergie aux cyclodextrines

- **Allergy to low dose sugammadex.**

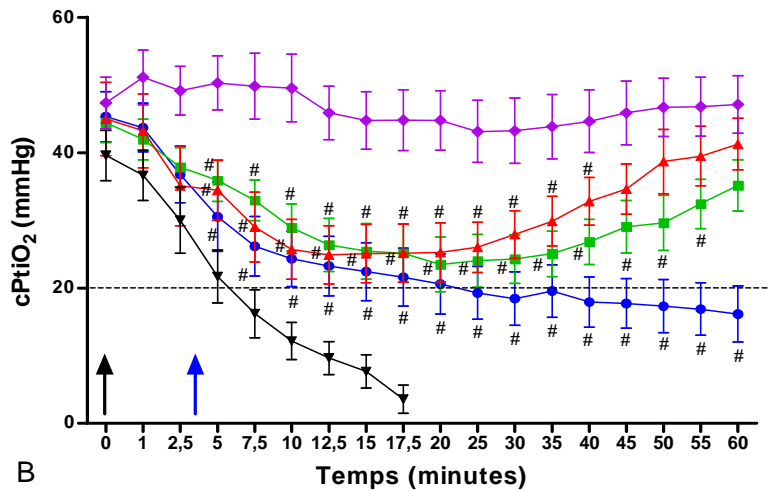
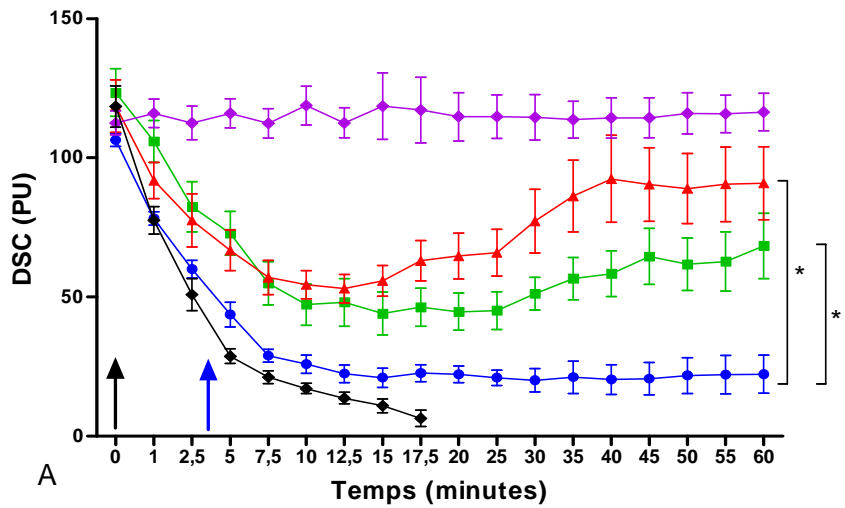
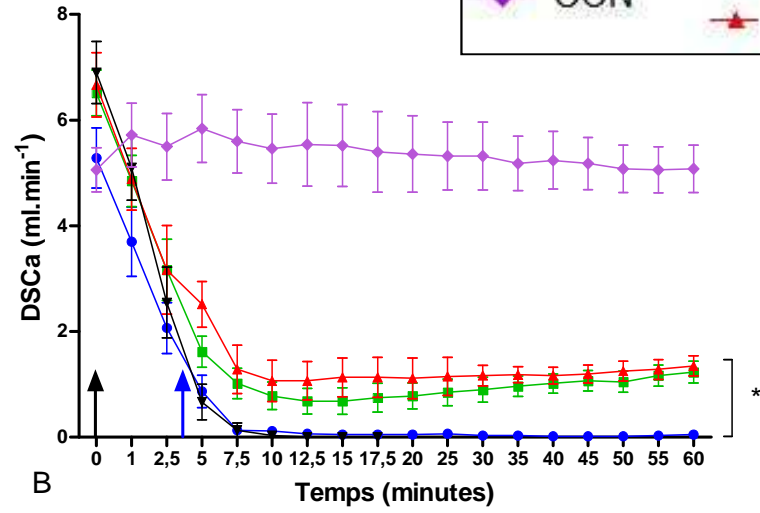
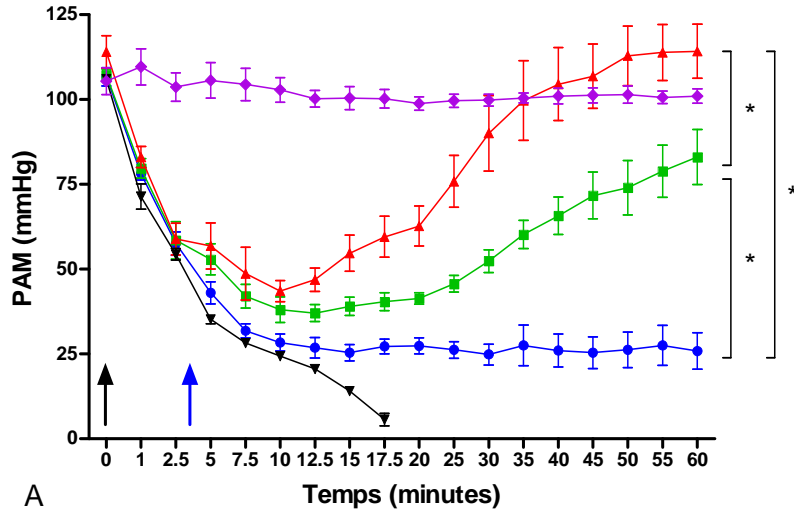
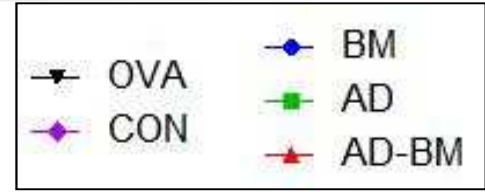
Homme 17 ans, grade II, prick +; *Menéndez-Ozcoidi*  
*Anaesthesia*. 2011 Mar;66(3):217-9.

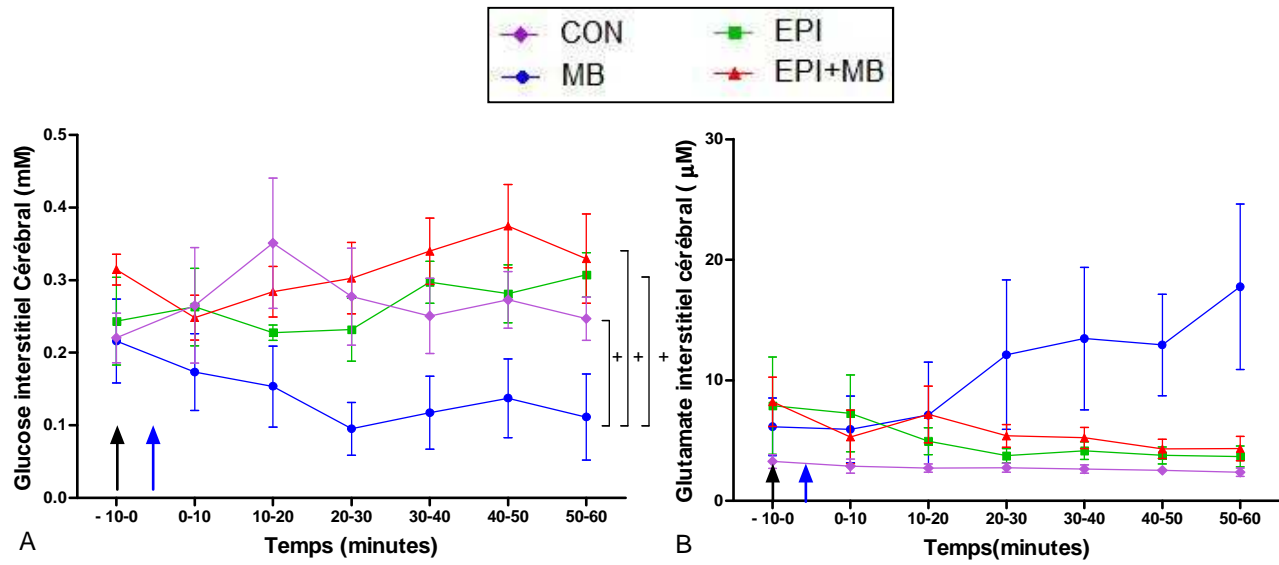
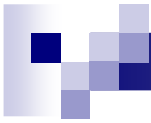
- **Three cases of suspected sugammadex-induced hypersensitivity reactions. Grade I prick +, Grade III prick +, Grade II no test.** *Godai et al, Br J Anaesth*. 2012 Aug;109(2):216-8



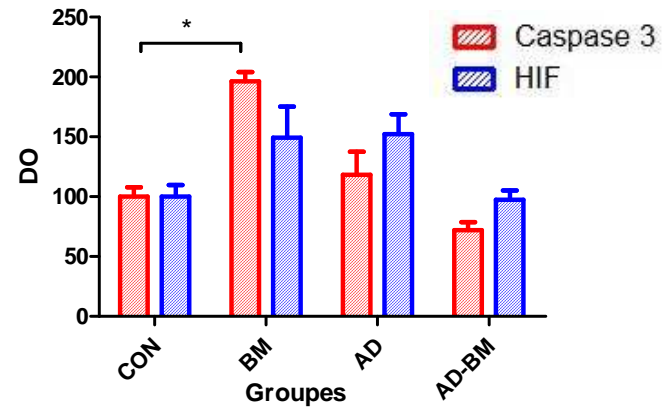


Vers de Nouveaux traitements?






### Expression de Caspase 3 et HIF - Cortex Cérébral






# **NMBAs, allergy and immunological dogma**



# Les limites de la conception classique de l'allergie « immédiate »

- La sensibilisation nécessite
  - Une **exposition préalable**: Latex food syndrome? Curares?
  - Une **hapténisation** pour les petites molécules: Curares? Sulfamides?
- La réaction est liée à une interaction **Ag/IgE**:
  - Allergie aux dextrans, à la chymopapaïne et IgG?
- La réaction résulte de l'activation des **basophiles et mastocytes** et de la libération d'**histamine**
  - Efficacité inconstante des anti-H1
- Le choc anaphylactique est **LE Choc Vasoplégique Type**
  - Echecs de la stratégie Adrénaline et remplissage



# L'anaphylaxie Médicamenteuse : un modèle

- *Neuromuscular blocking drugs and  $\beta$ -lactams, have perhaps been the most studied of the drugs known to cause type 1 hypersensitivity reactions in man...*
- *NMBDs demonstrate a number of intriguing departures from the currently accepted explanations of the mechanisms underlying the allergic immune response to 'small' molecules such as drugs and simple chemicals...*



## PHYSIOLOGY OF NEUROMUSCULAR TRANSMISSION AND BLOCKADE

- NMBAs are divalent ammonium compounds which bind to the  $\alpha$  subunit of the ACh receptor.
- Depolarizing (non-competitive) NMBAs: ***succinylcholine***
- Non-depolarizing (competitive) NMBAs:
  - Aminosteroid : ***pancuronium, vecuronium, rocuronium***
  - Benzylisoquinolinium : ***mivacurium, atracurium, cis-atracurium***



# **DIVERSITY OF HYPERSENSITIVITY REACTIONS TO NMBAs**





# **Non-IgE Mediated Reactions**





# Histamine Release

- Benzylisoquinolinium > Aminosteroid NMBAs

- Atracurium
- Mivacurium

But :

- Rapacuronium : histamine release 
- Cis-atracurium : histamine release 

# A Mechanism for Rapacuronium-induced Bronchospasm

## M2 Muscarinic Receptor Antagonism

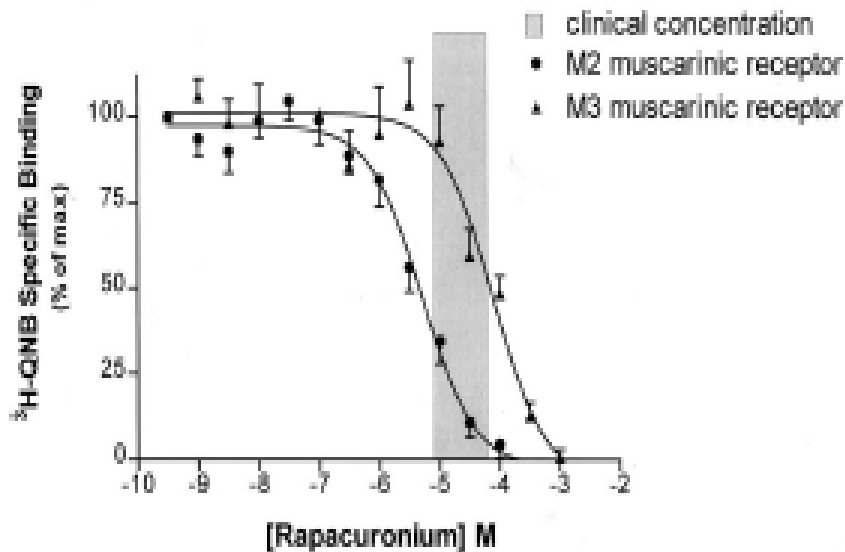


Fig. 1. Competitive displacement of  $^3\text{H}$ -QNB by rapacuronium in membranes prepared from Chinese hamster ovary cells expressing the M2 or M3 muscarinic receptor. The affinity of rapacuronium for the M2 muscarinic receptor was higher than its affinity for the M3 muscarinic receptor and was within clinically relevant concentrations. ( $n = 6$  for M2, and  $n = 8$  for M3.)

- Rapacuronium has a higher affinity for M2 muscarinic receptors as compared with M3 muscarinic receptors.

- Blockade of M2 muscarinic receptors on prejunctional parasympathetic nerves

  - ➔ increased release of acetylcholine

  - ➔ M3 muscarinic receptor-mediated airway smooth muscle constriction



# L'allergie aux curares

- Mécanisme
  - IgE médié: 72%
  - groupements ammoniums IV et/ou amines tertiaires
- Sans antécédent d'exposition à un curare
  - 15 à 75% selon les études
  - Difficile à évaluer (traçabilité...)
  - Facteurs environnementaux?
  - Autres ammoniums quaternaires?
  - Pholcodine?



# Substituted ammonium ions as allergenic determinants in drug allergy

- ... **Alcuronium-reactive antibodies** were found in five drug-sensitive subjects and most of the antibodies **cross-reacted** with other muscle relaxants and with a variety of apparently structurally unrelated drugs
- ... Structure-activity studies designed to explore the molecular basis of the antibody binding established that **quaternary and tertiary ammonium** ions were the complementary allergenic sites on the reactive drugs...
- ... Sensitivity might be established by **prior exposure to substituted ammonium groups** on a compound that is otherwise structurally **unrelated to the NMBAs**. Such compounds are many, widely distributed and often contacted in everyday activities.



# IgE-cross linking

- Multivalent drug -- carrier complexes are said to be a requirement for cross-linking of mast cell-bound IgE .
- NMBAs did not bind to plasma proteins
- The substituted ammonium ions of NMBAs:
  - are responsible for neuromuscular blocking and allergenic properties
  - are at a distance from 1 to 1.45 nm
- Divalency of NMBAs could explain allergen-induced mediator release in a sensitized subject even in the absence of protein binding.



**Are there differences  
between NMBAAs?**



## Incidence of anaphylaxis according to the NMBA over 6 years in France (1997 – 2003)

Rocuronium	1 :	5,100
Succinylcholine	1 :	5,500
<hr/>		
Vecuronium	1 :	13,000
Pancuronium	1 :	14,700
<hr/>		
Mivacurium	1 :	38,000
Atracurium	1 :	52,800
Cisatracurium	1 :	149,000





**How can we explain these differences between drugs?**



# Results from skin-test investigations

- Patients may react with :
  - **All** NMBAs → *a single overwhelmingly dominant allergenic determinant structure quaternary ammonium determinant (alcuronium)*
  - **A single** NMBAs or **Several** NMBAS with or without class effect → *neighboring groups of different structures on the different NMBAs, in addition to the substituted ammonium groups, form part of the allergenic determinant structure*



# Quantitative hapten inhibition

- The correlation between the drug that produced the allergic reaction and cases where the same drug was also the strongest inhibitor, ignoring the drug-solid phase employed, was only about **fifty percent**.
- In the absence of a match between the NMBA-solid phase and the provoking NMBA , the clinical relevance of inhibition data is generally lacking
- However, when the NMBA that produced the anaphylaxis matches the NMBA on the solid phase, inhibition results with other NMBAs may, sometimes at least, reveal which of the drugs, if any, are sufficiently cross-reactive to also cause an allergic reaction in the patient.



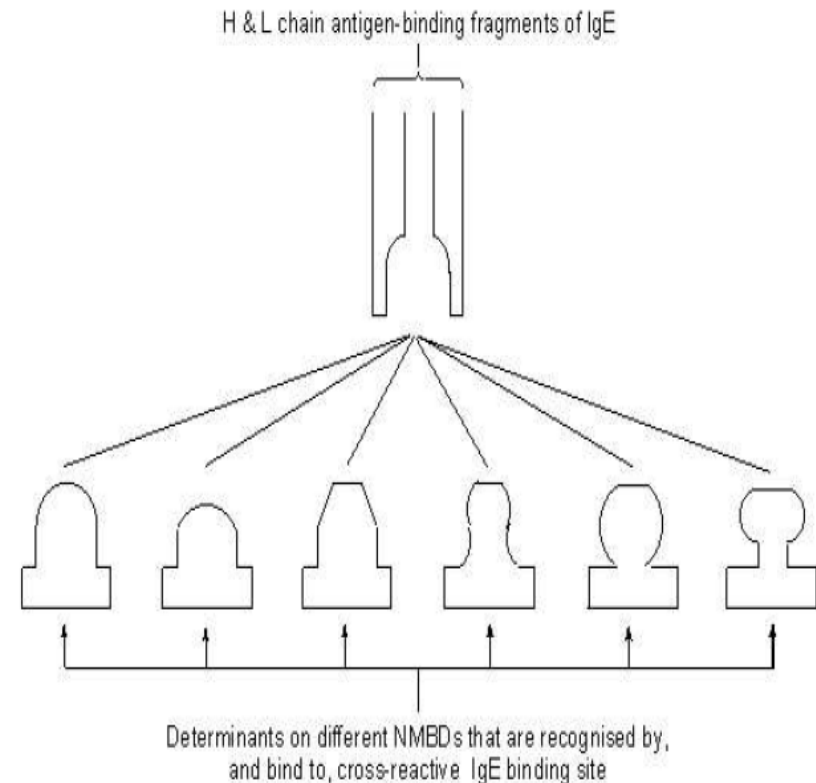
# Specificities of NMBA-reactive IgE antibodies

- Structures adjoining or adjacent to the substituted ammonium groups are almost certainly recognised by some antibodies from allergic patients
- Antibodies from different patients show different recognition spectra when tested with the different NMBAs and other reactive compounds.
- Observed patterns of reactivity can be wide:
  - recognition of only one NMBA, e.g. alcuronium
  - strong reactions with all NMBAs.
  - reaction with only two or three or more of the NMBAs

# Specificities of NMBA-reactive IgE antibodies

- NMBD recognition may be due to antibody combining sites of quite broad specificity that accommodate different substituted ammonium groups (methyl, ethyl.... etc) alone or sometimes with some nearby structures on the NMBDs.

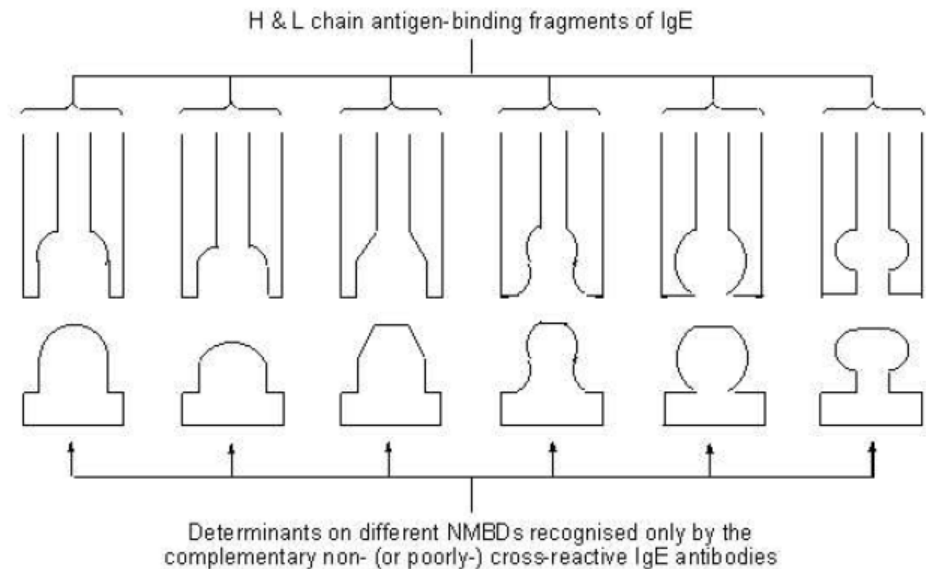
a. Different NMBDs each recognised by the same (cross-reactive) IgE antibody:



# Specificities of NMBA-reactive IgE antibodies

- Existence of different populations of antibodies that each recognise a different NMBD with little or no cross-reactivity with other NMBDs.
- Such heterogeneous populations of different antibodies collectively demonstrating a range of different combining site specificities would, together, recognize most, or all of, the NMBDs.
- Such antibodies would recognize different NMBDs via the substituted alkyl group (methyl, ethyl etc) and/or by co-recognition of neighbouring structures thus minimizing cross-reactivity.

b. Same NMBDs each recognised by a different (non-cross-reactive) IgE antibody:





# Nomenclature chimique (I)

(définitions IUPAC)

## ■ Amines :

- composés dérivés formellement de l'ammoniac ( $\text{NH}_3$ ) en remplaçant 1, 2 ou 3 atomes d'hydrogène par des groupements hydrocarbonés.
- *Amine primaire* :
  - Structure générale  $\text{R-NH}_2$
- *Amine secondaire* :
  - Structure générale  $\text{R}_2\text{-NH}$
- *Amine tertiaire* :
  - Structure générale  $\text{R}_3\text{N}$

Source : IUPAC Compendium of Chemical Terminology, 2<sup>nd</sup> Edition, 1997.

# Nomenclature chimique (II)

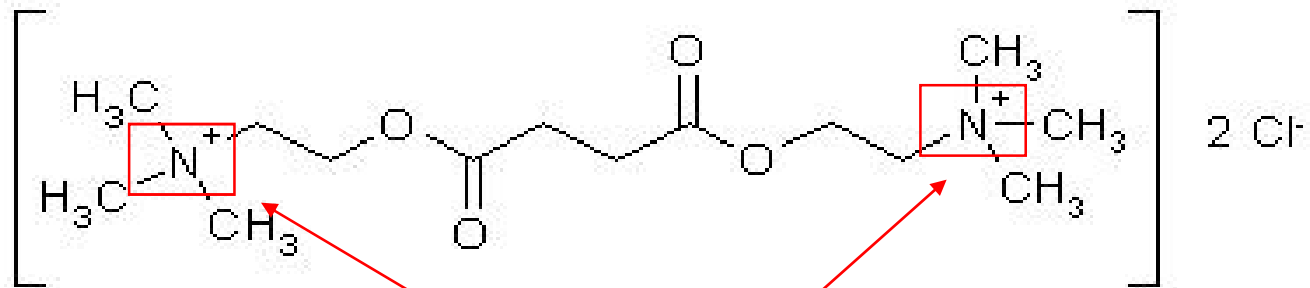
(définitions IUPAC)

## ■ Ammoniums :

- Structure générale :  $\text{NH}_4^+ \text{Y}^-$
- *Ammoniums quaternaires* : dérivés des ammoniums, dans lesquels **tous** les atomes d'hydrogène (4) liés à l'azote ont été remplacés par des groupements hydrocarbonés.
- *Iminiums* : sels dans lequel le cation a la structure :  $\text{R}_2\text{C}=\text{N}^+\text{R}_2 \text{Y}^-$
- *Aminiums (ammoniums non-quaternaires)* : cations  $\text{HR}_3\text{N}^+$  formés par la protonation d'une amine  $\text{R}_3\text{N}$ .



# Curares dépolarisants

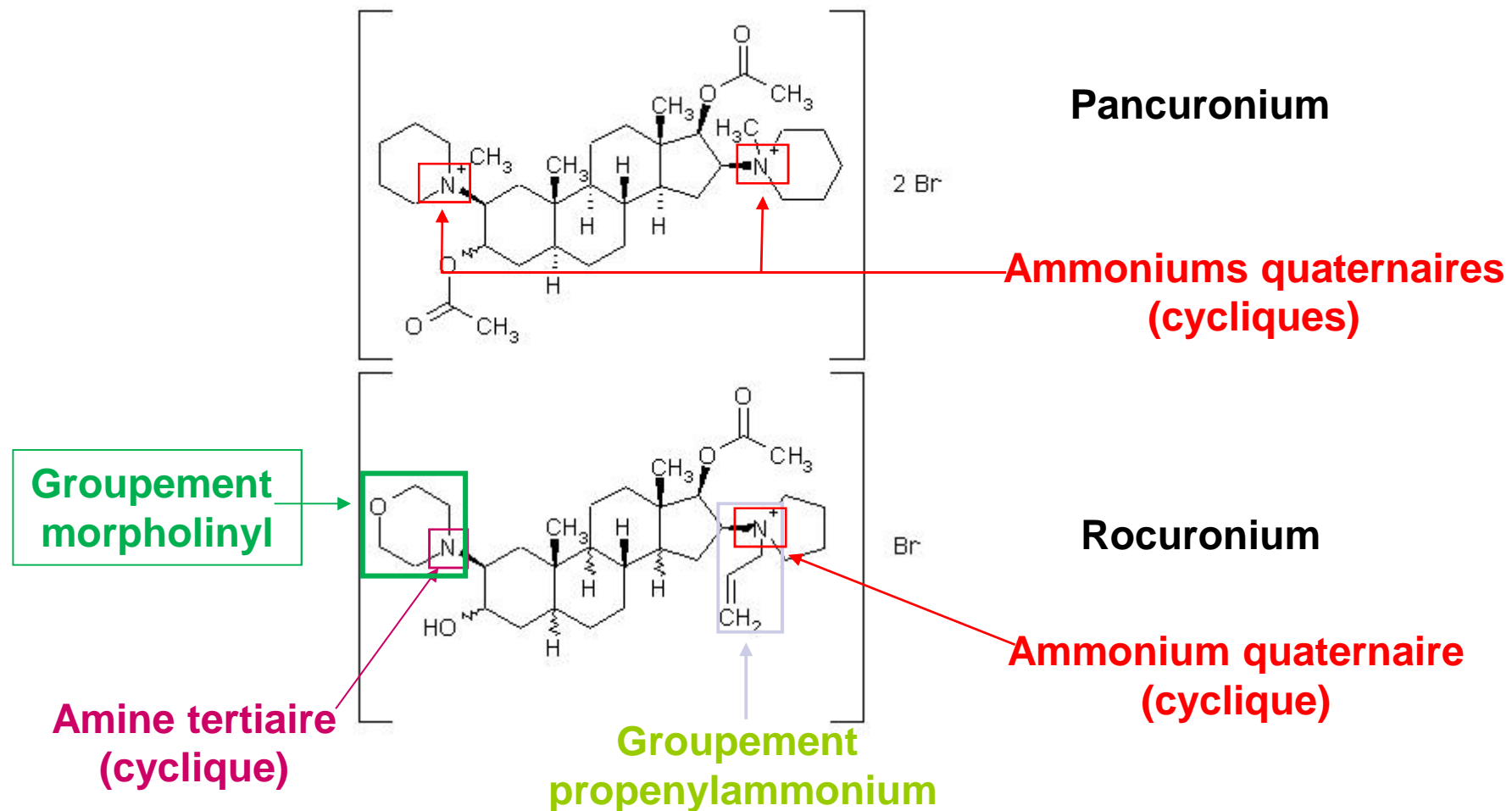


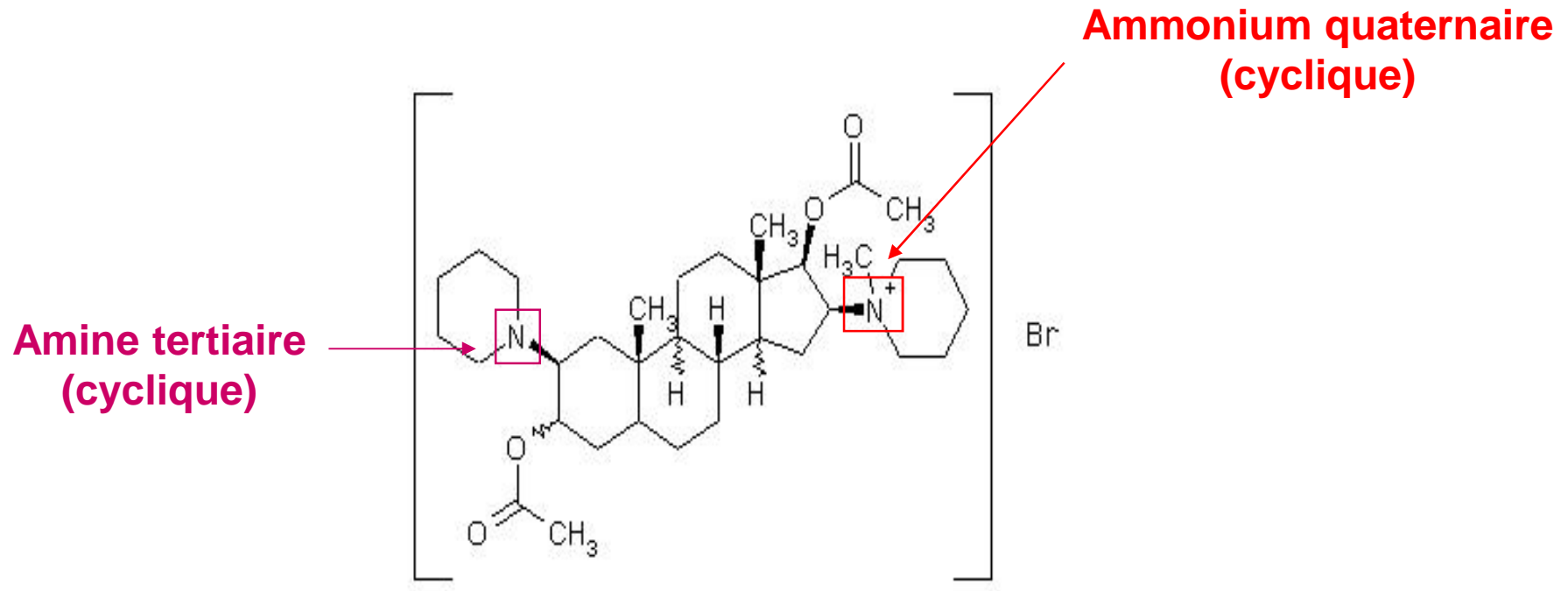
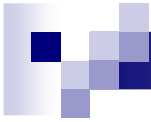
Ammoniums quaternaires

**Suxaméthonium**

# Curares non dépolarisants

## ■ Type aminostéroïdes

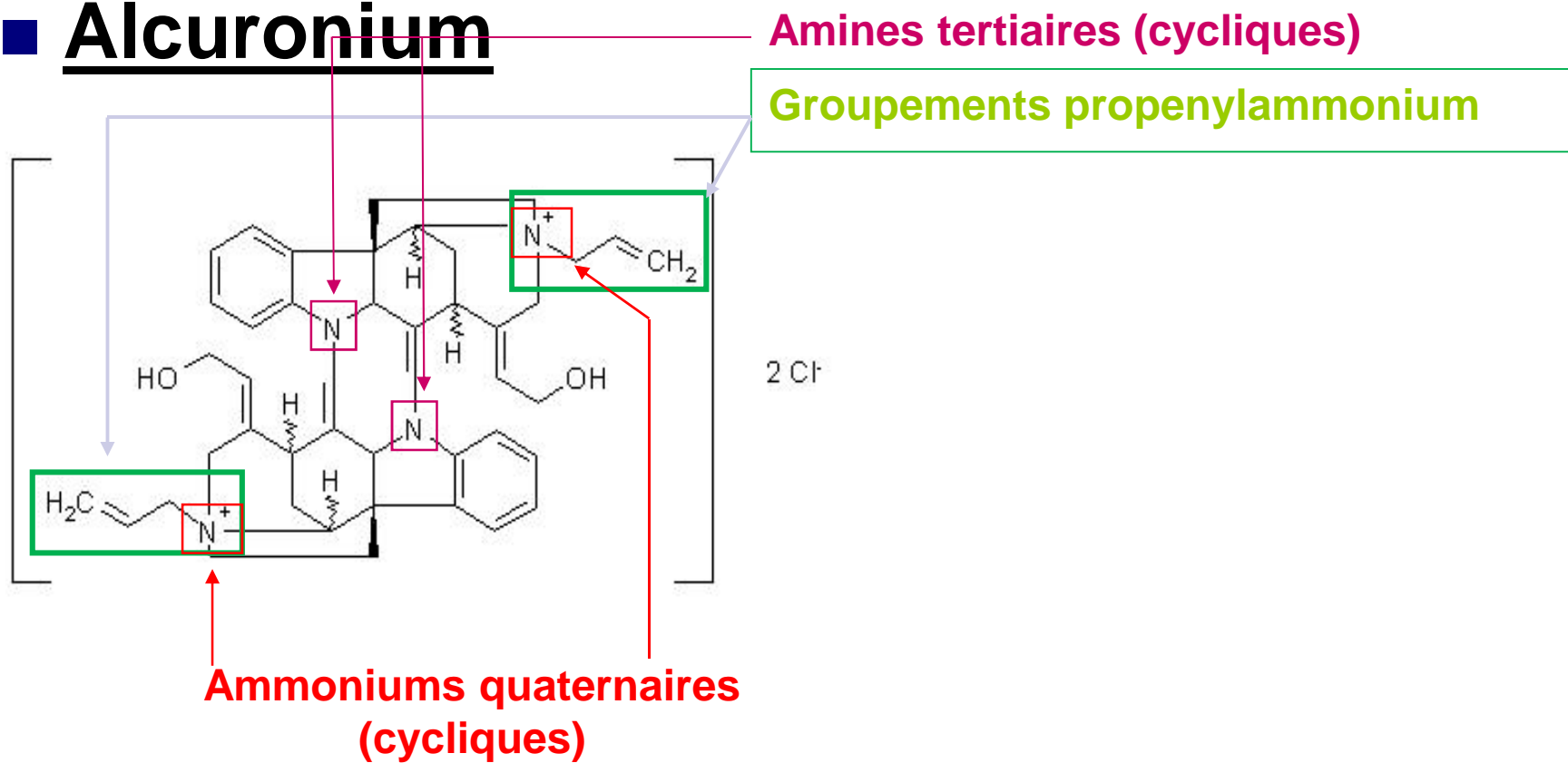




**Vécuronium**

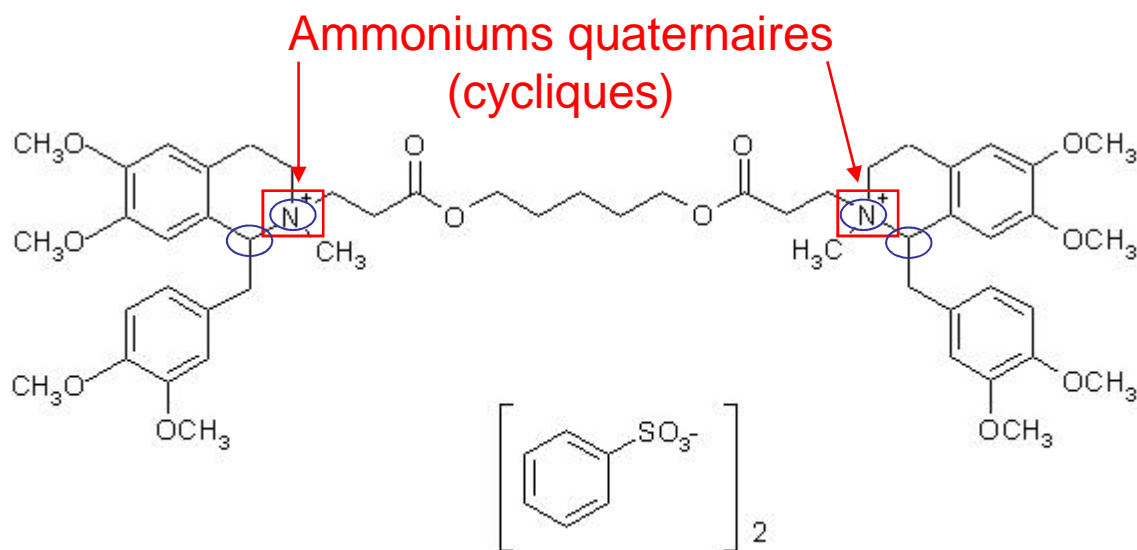
# Curares non dépolarisants

## ■ Alcuronium



# Curares non dépolarisants

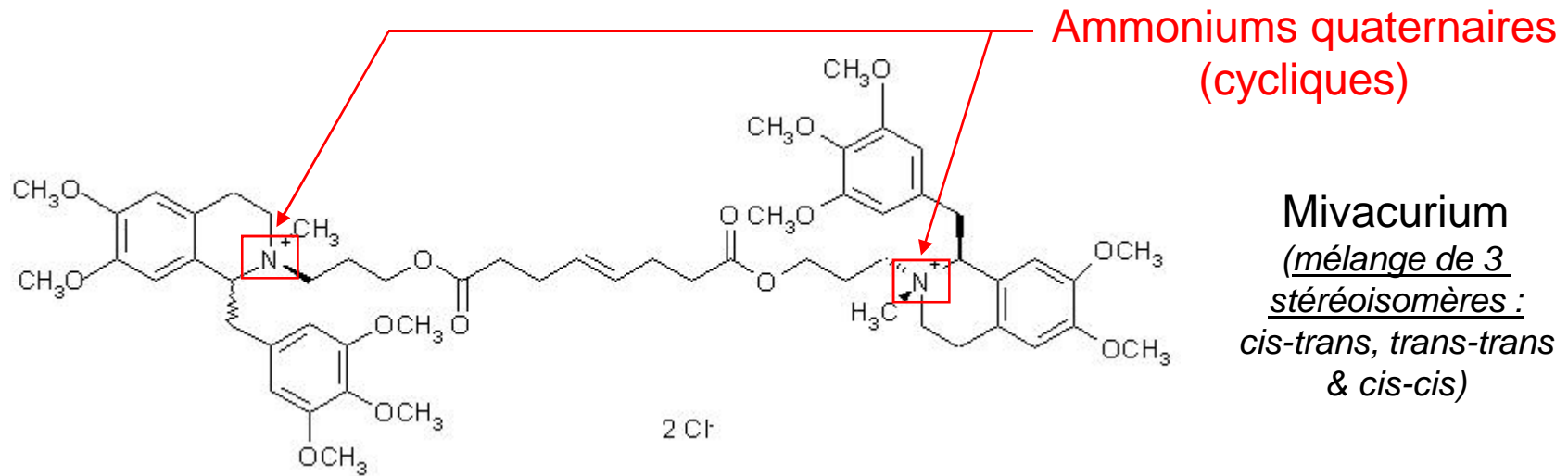
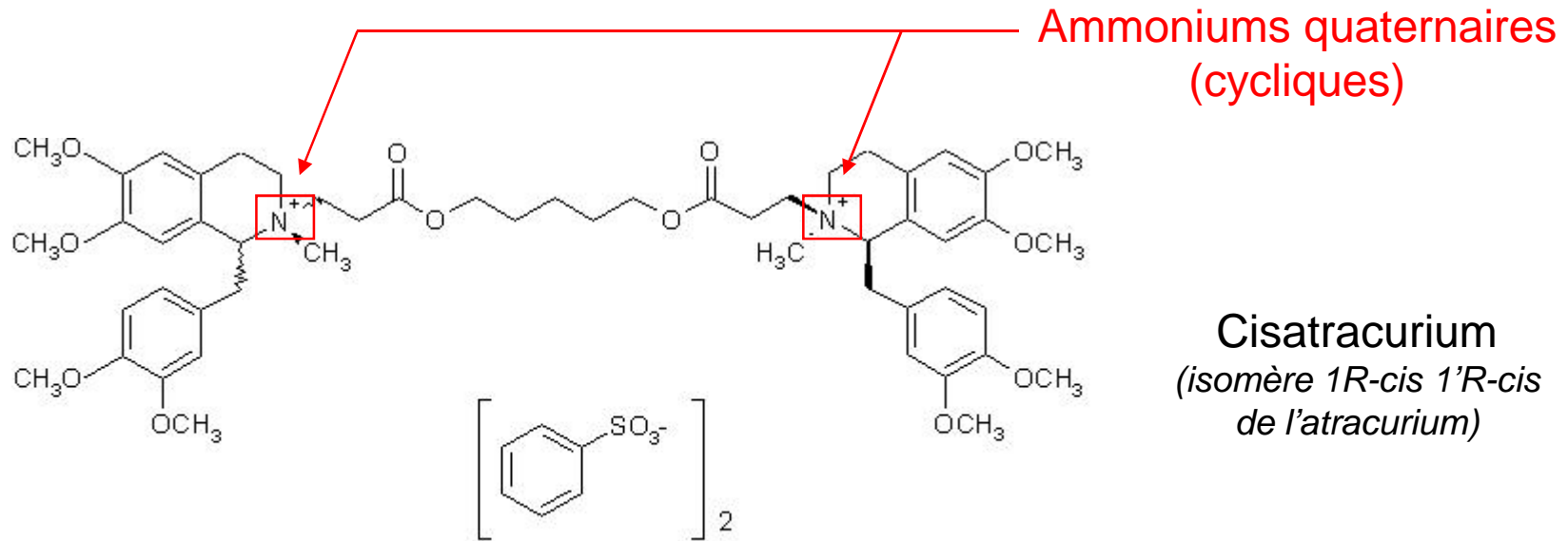
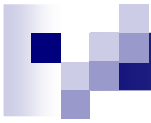
## ■ Type benzylisoquinolines



Atracurium

*(mélange de 10 stéréoisomères)*

○ = centres chiraux (4)





# Previous Exposure

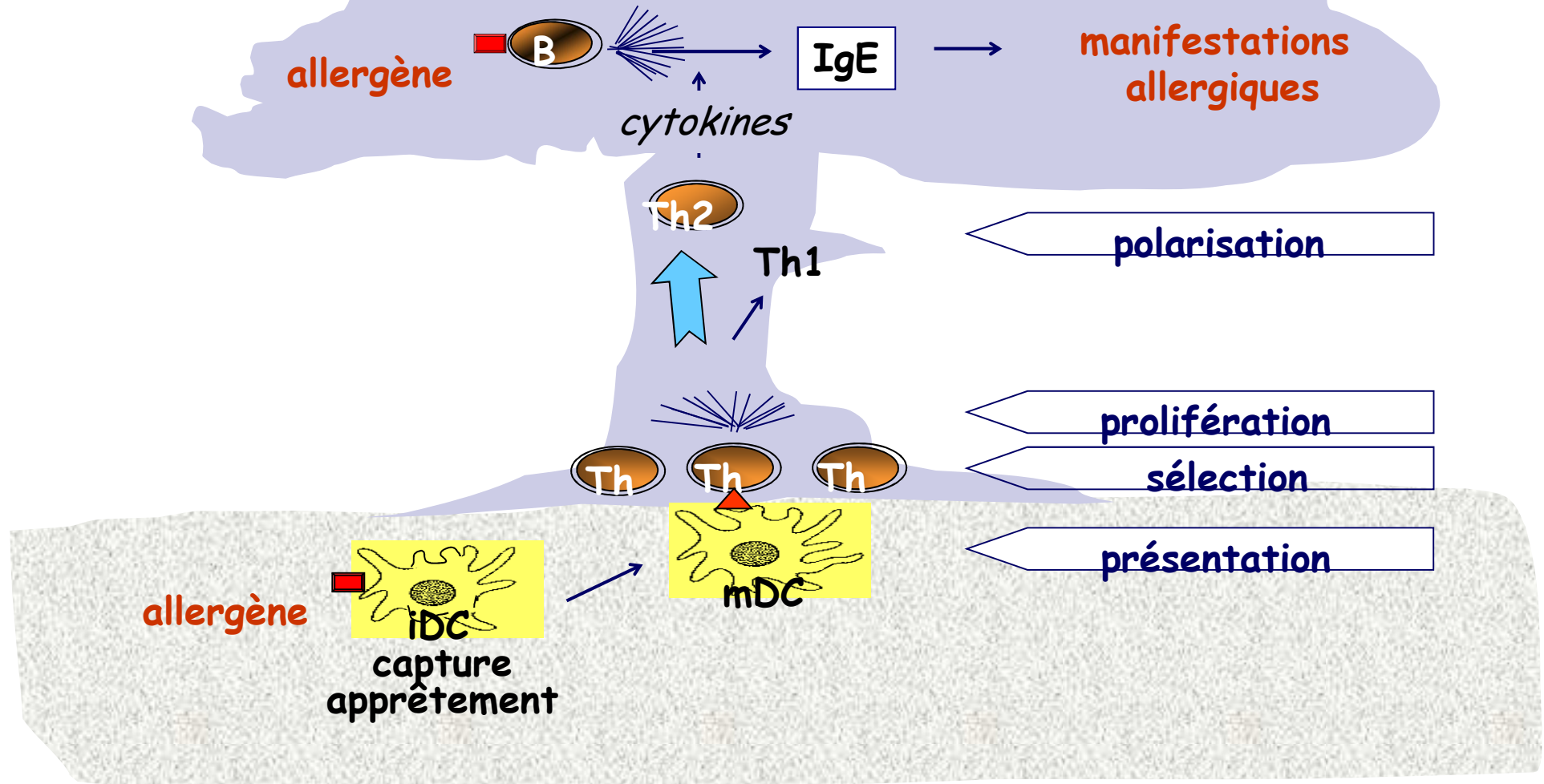
- IgE-mediated reactions after exposure to a drug are generally assumed to be due to the prior sensitization of the allergic subject by the drug
- But : lack of previous exposure
  - At least **17%** in France
  - Up to **75%** in Australia



# **Mécanisme de la sensibilisation**



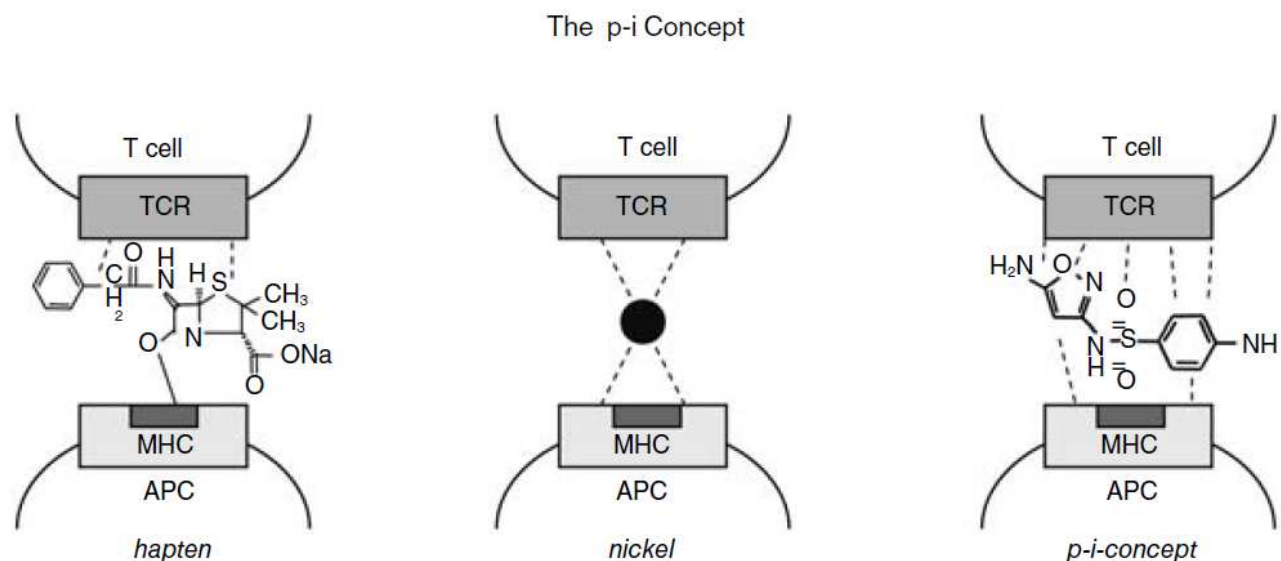
# réponse immune contre l'allergène chez le sujet atopique



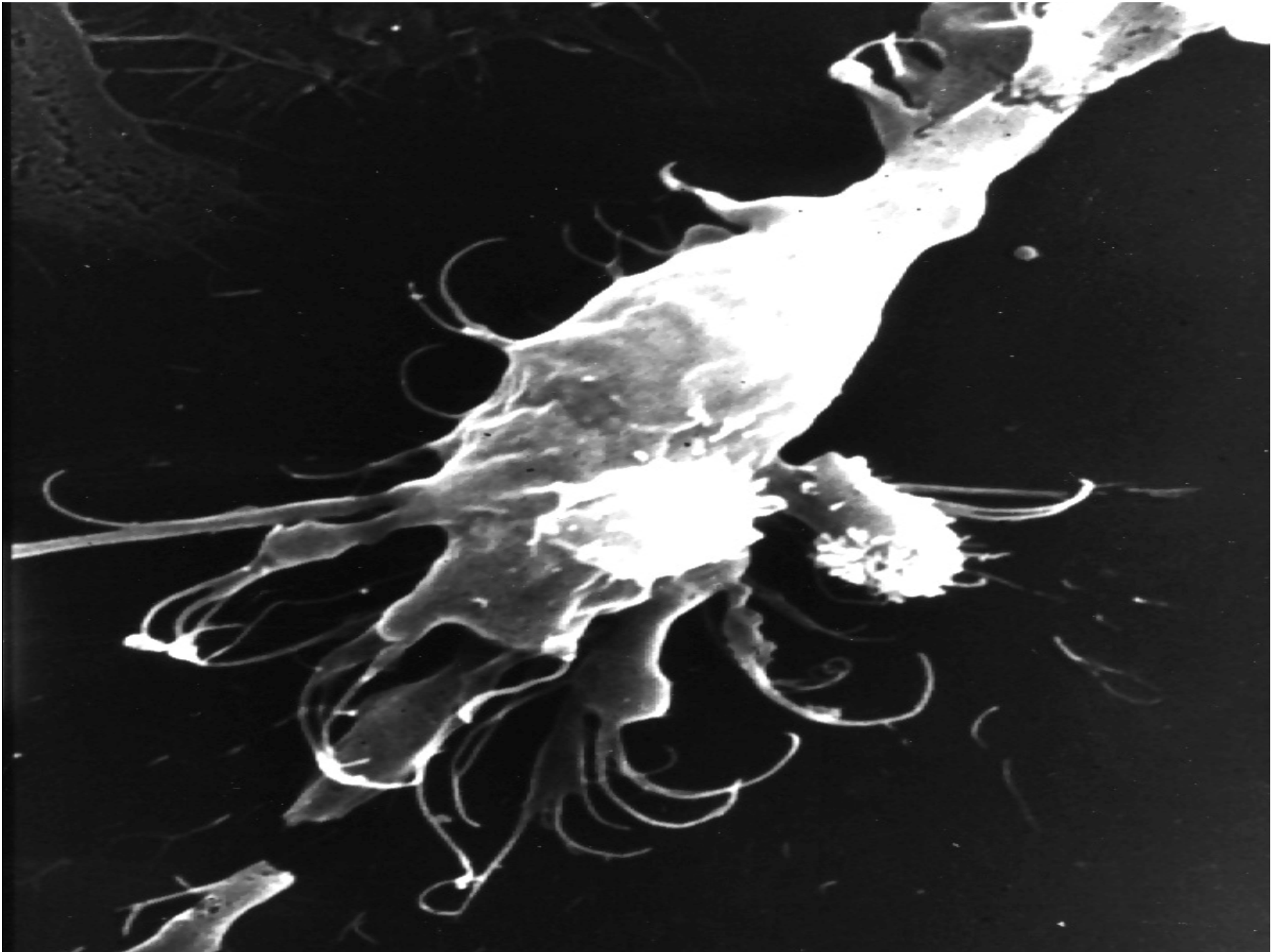


# **Hapten and Small Molecules**

# Pharmacological Interaction of Drugs with Immune Receptors: The p-i Concept

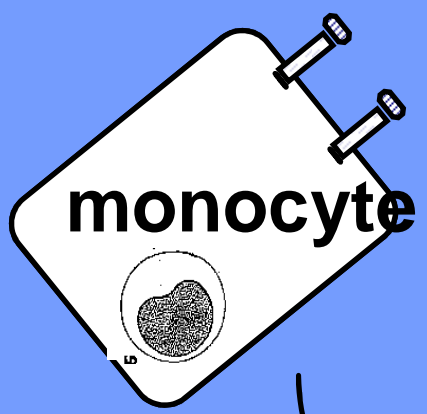


**Fig. 1** A comparison of different small antigens stimulating T-cells via the hapten, a hapten-like and the p-i mechanism. Penicillin, nickel ions (black ball), and SMX serve as the respective examples. Strong, covalent bonds between the antigens and the MHC and the TCR are indicated by solid lines, while weaker, noncovalent interactions are depicted as dashed lines. For haptens, the majority of the antigen-binding energy stems from the interaction with the MHC-peptide complex via few but strong covalent bonds (hapten; note that certain haptens may be strongly associated not only with the MHC but the TCR as well).<sup>65</sup> Ni may interact either like a non-covalent hapten,<sup>17</sup> or as depicted here,<sup>16</sup> forming equally strong, non-covalent interactions with both MHC and TCR (nickel), while at least some drugs would derive the majority of their binding energy from weak, non-covalent interactions with the TCR (p-i-concept). These different modes of interaction represent a continuum of possibilities, with the (pro)hapten mode on one extreme of the spectrum, the p-i-concept mode representing the other extreme, and the Ni mode as an intermediate possibility.

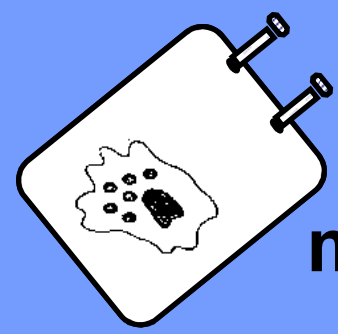
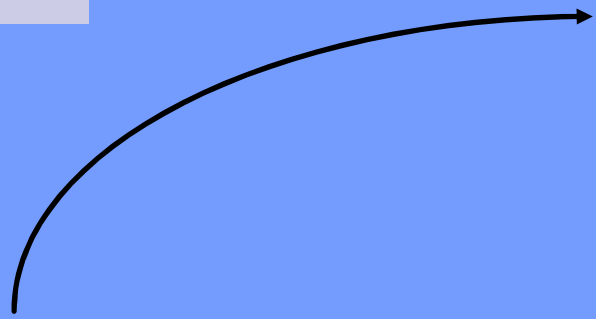


**day 0**

**day 5-7**

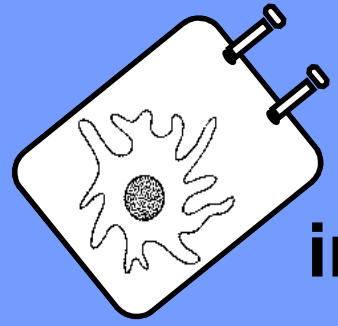


**monocyte**



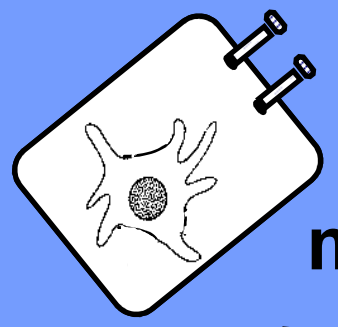
**macrophage-like cell**

**IL-4**



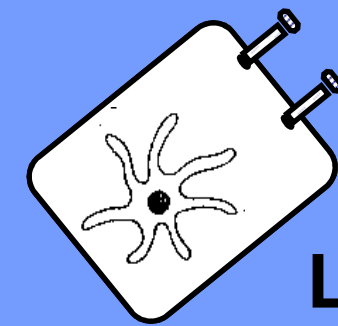
**immature DC**

**IL-4  
TNF- $\alpha$   
PGE2**



**mature DC**

**IL-4  
TGF- $\beta$**



**Langerhans-like DC**



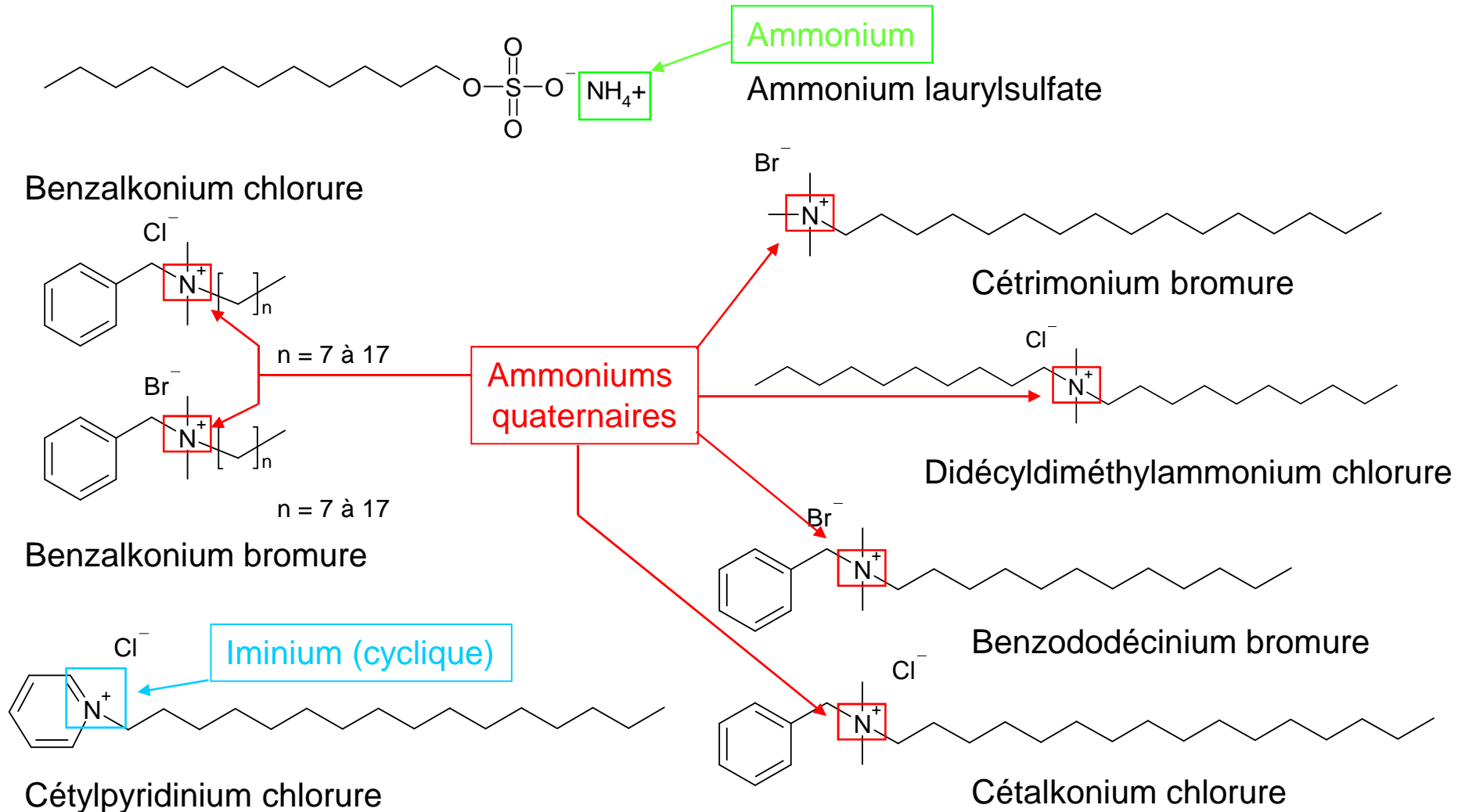
**What can be the antigenic  
source of NMBA-reactive IgE  
antibodies?**



# Environmental agents

- Compounds containing tertiary amine or quaternary ammonium groups occur widely in drugs, cosmetics, disinfectants, industrial materials, foods...
- Only a small number of cases of anaphylaxis apparently provoked by environmental agents have been reported
- **The theory of environmental sensitization remains unproven and difficult to establish.**

# Exposition "environnementale" aux ammoniums quaternaires (II)



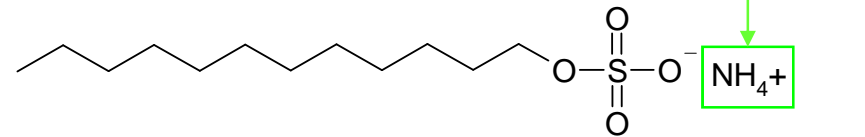


# Exposition “environnementale” aux ammoniums quaternaires (III)

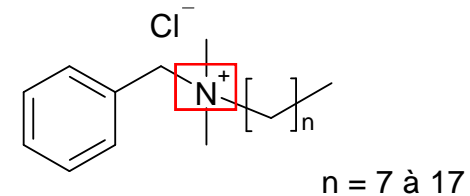
## ■ Voie cutanée

### □ *Produits cosmétiques :*

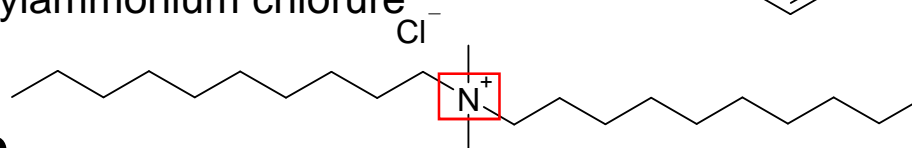
- Ammonium laurylsulfate



- Benzalkonium chlorure (principe actif : MERCRYL®)



- Didécyldiméthylammonium chlorure



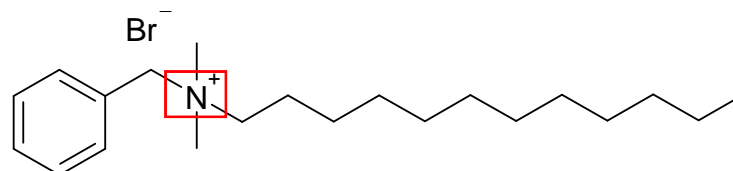
## ■ Voie ophtalmique

### □ *Collyres :*

- Benzalkonium chlorure (excipient : ACULAR®, XALATAN®)
- Benzododécinium bromure (excipient : TIMOPTOL®)

### □ *Solutions pour lavage ophtalmique :*

- Benzododécinium bromure (excipient : DACRYOSERUM®)



# Exposition “environnementale” aux ammoniums quaternaires (IV)

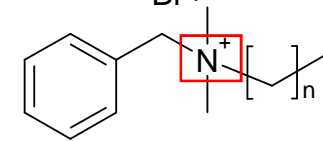
## ■ Voie nasale

### □ *Suspensions nasales :*

- Benzalkonium chlorure (excipient : BECONASE®, NASACORT®)

### □ *Spray nasal :*

- Benzalkonium bromure (principe actif : EUVANOL®)

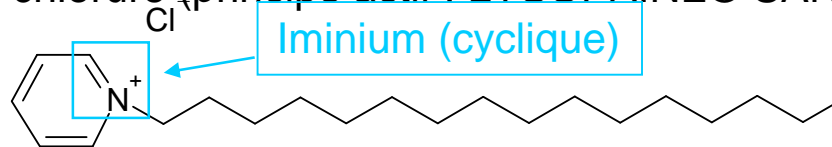


n = 7 à 17

## ■ Voie buccale

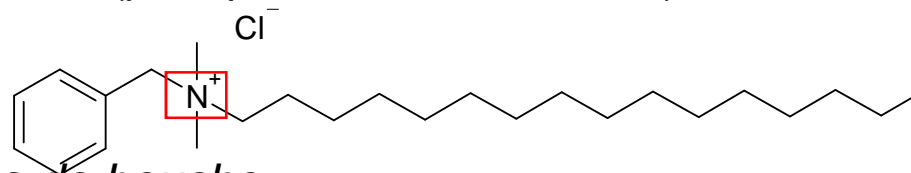
### □ *Comprimés :*

- Cétalpyridinium chlorure (principe actif : LYSOPAINE® SANS SUCRE)



### □ *Gel buccal :*

- Cétalkonium chlorure (principe actif : PANSORAL®)



### □ *Solution pour bains de bouche :*

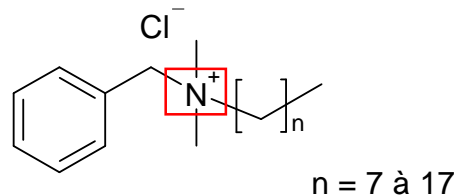
- Cétalpyridinium chlorure (principe actif : ALODONT®)

# Exposition “environnementale” aux ammoniums quaternaires (V)

## ■ Voie vaginale

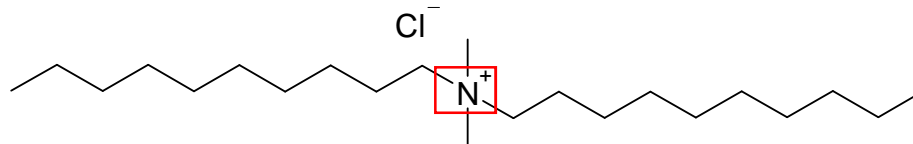
□ *Crèmes vaginales :*

- Benzalkonium chlorure (principe actif : PHARMATEX®)



## ■ Voie cutanée / pulmonaire (désinfectants)

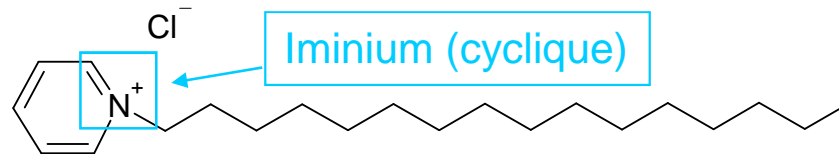
- Didécyl diméthylammonium chlorure (divers produits ANIOS®)



# Exposition “environnementale” aux ammoniums quaternaires (VI)

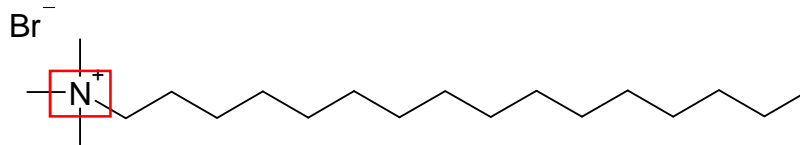
## ■ Voie entérale

- Cétalpyridinium chlorure (excipient : VICKS® sirop pectoral)



## ■ Voie parentérale (vaccins)

- Cétrimonium bromure (excipient : AGRIPPAL®, INFLUVAC®)



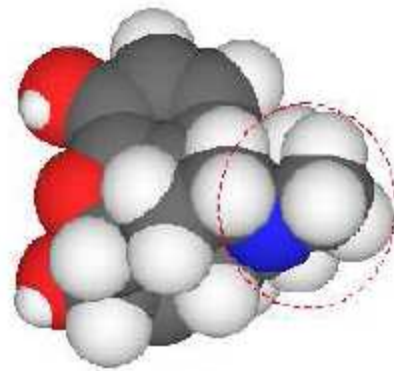


# L'hypothèse environnementale

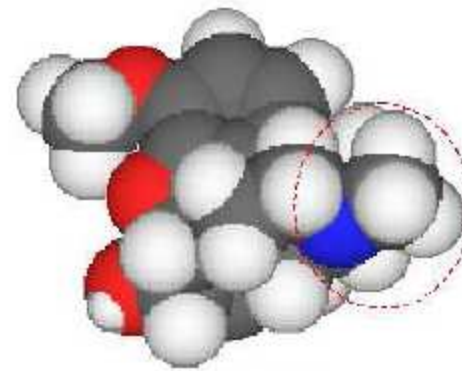
- Les réactions d'hypersensibilité immédiate aux produits de l'environnement sont rares
- La capacité de ces substances à induire une sensibilisation aux curares reste à démontrer



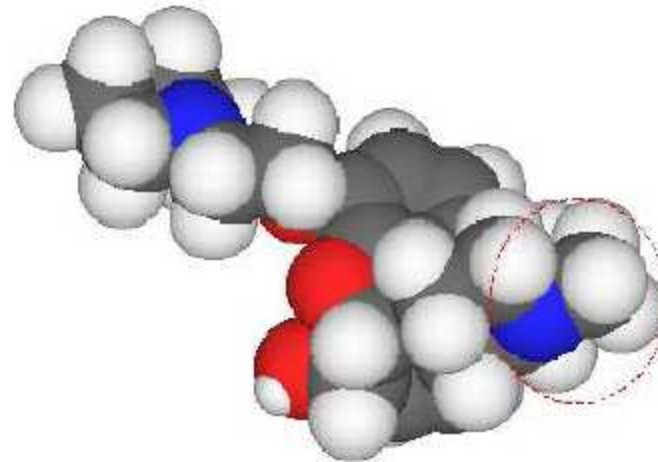
# The Pholcodine Hypothesis



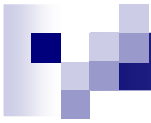
Morphine



Codeine



Pholcodine



# The Pholcodine hypothesis

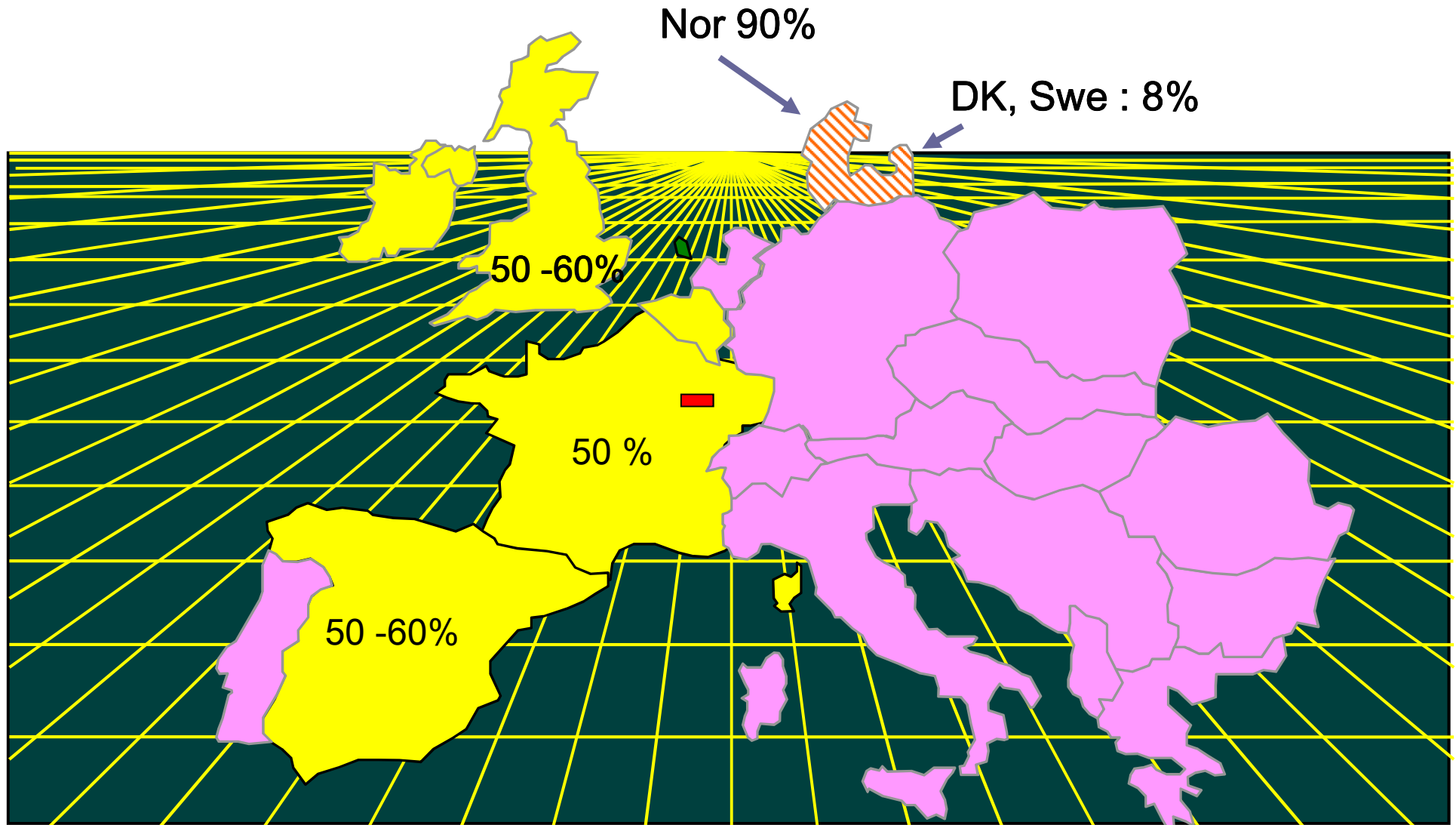
Erik Florvaag MD PhD

Haukeland University Hospital &  
University of Bergen,



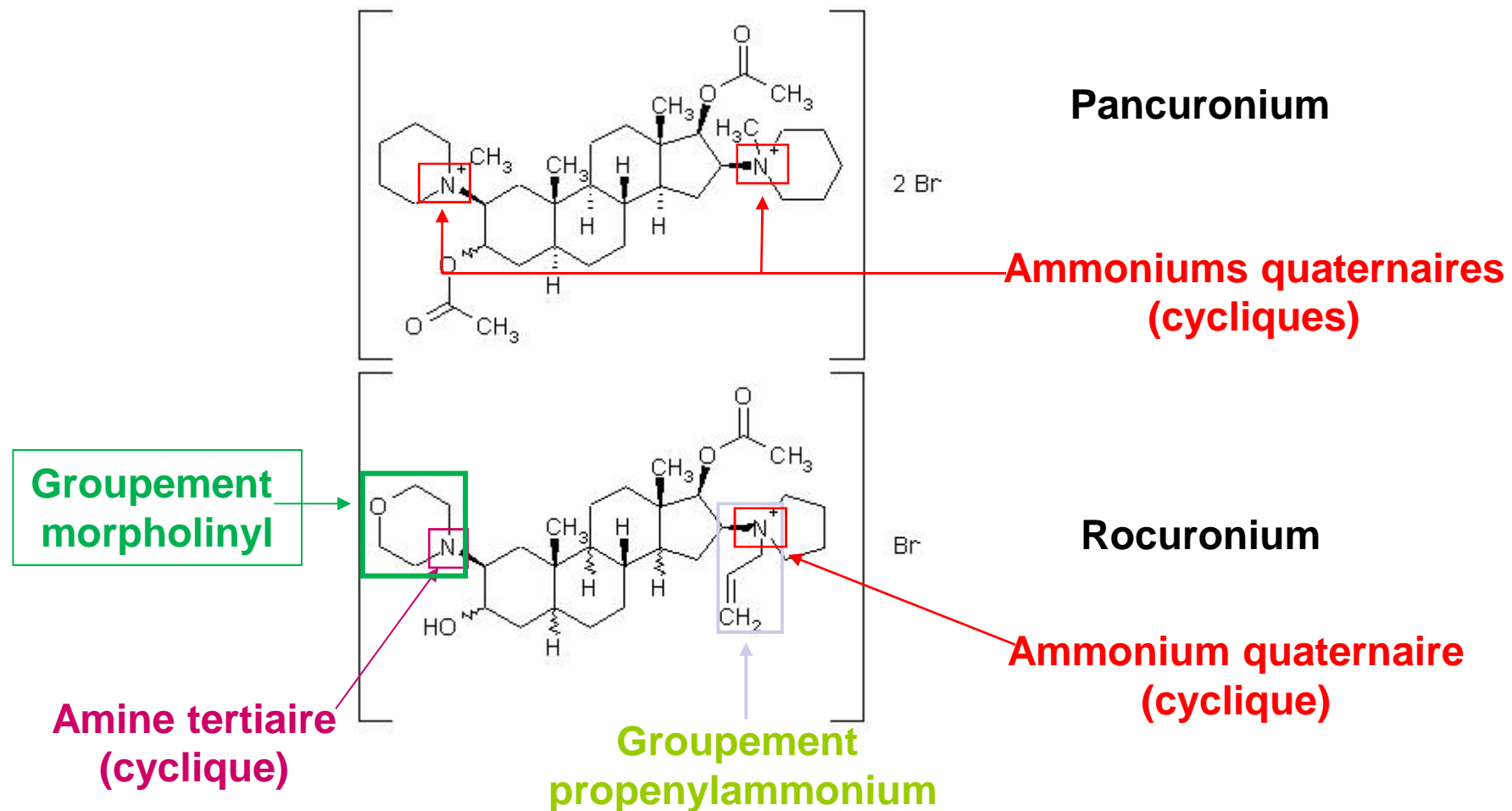


# Estimated Incidence

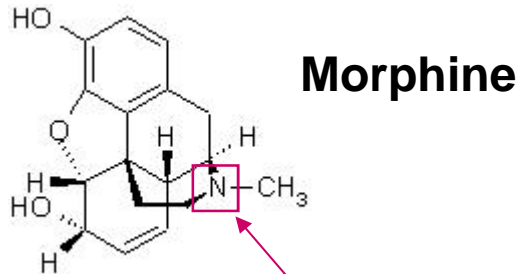


# Curares non dépolarisants

## ■ Type aminostéroïdes

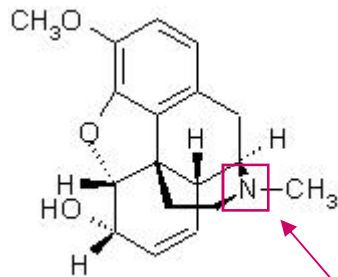


# Morphiniques



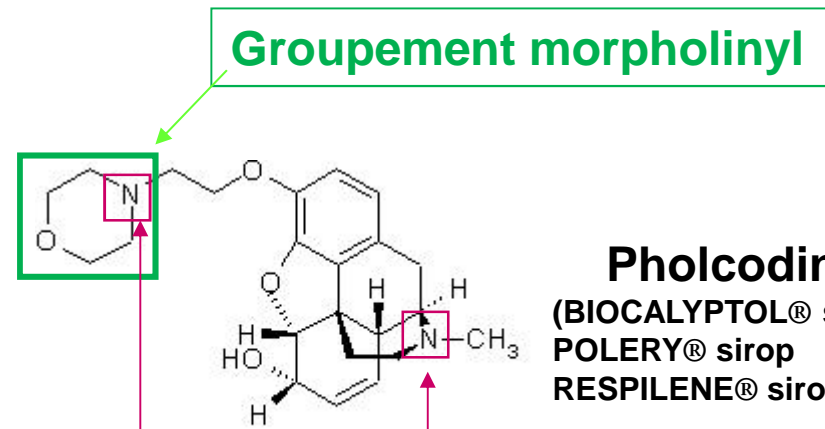
**Morphine**

Amine tertiaire  
(cyclique)



**Codéine**

Amine tertiaire  
(cyclique)



Groupement morpholinyl

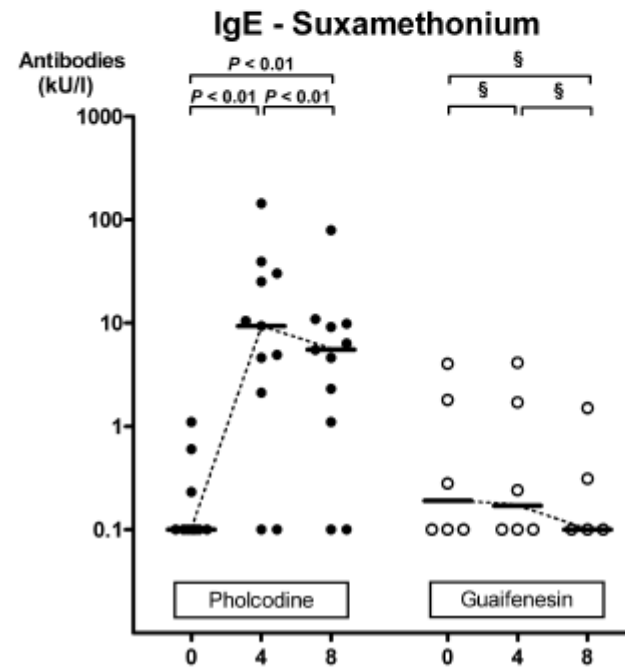
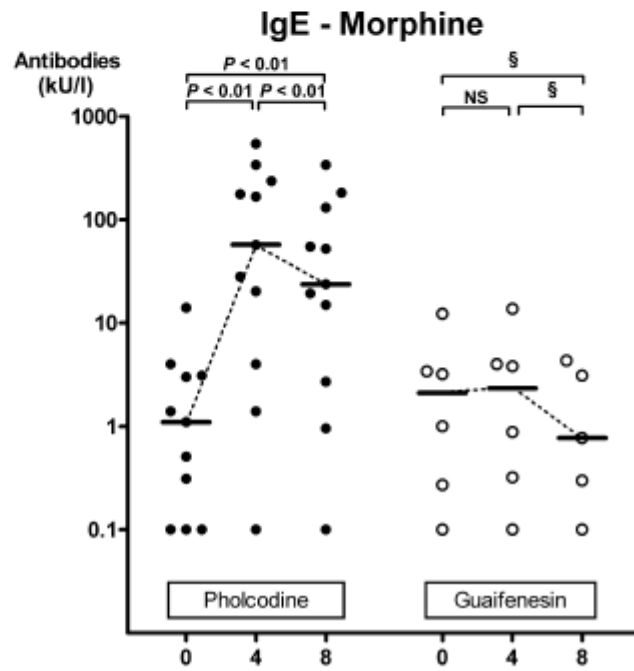
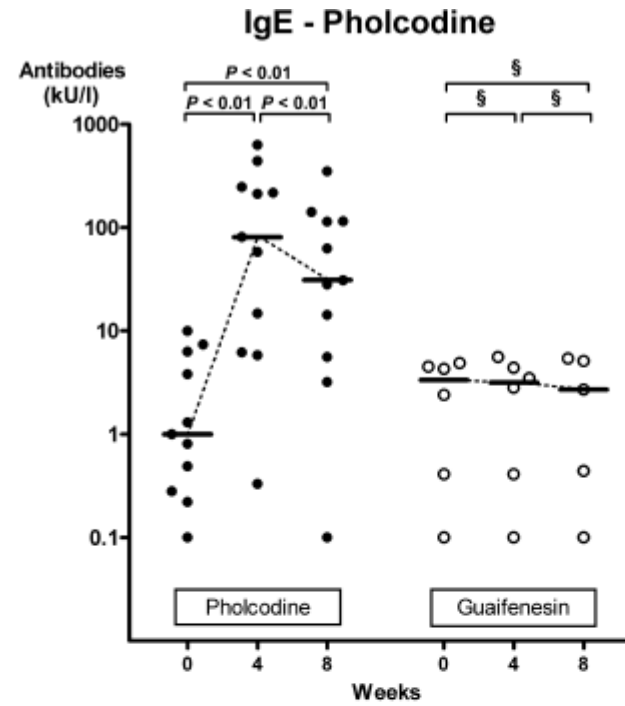
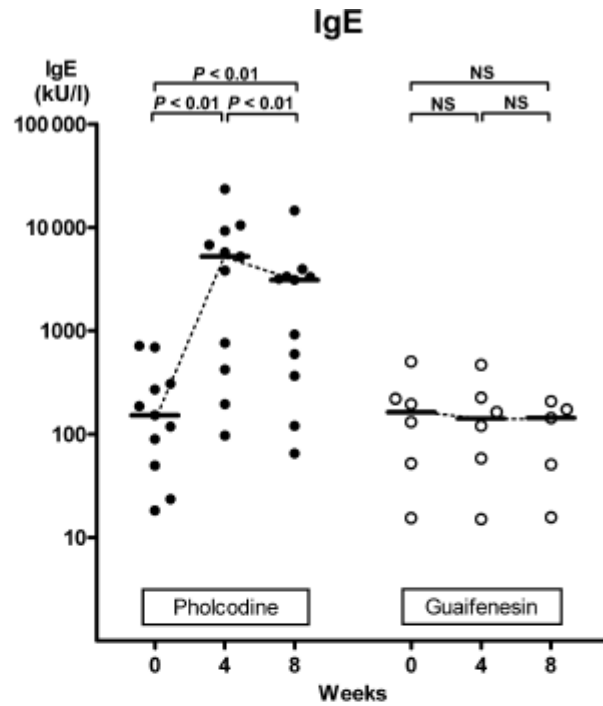
**Pholcodine**  
(BIOCALYPTOL® sirop  
POLERY® sirop  
RESPILENE® sirop...)

Amines tertiaires  
(cycliques)



# The Pholcodine Hypothesis

- Anaphylactic reactions to NMBA are six times more common in Norway than in Sweden
- IgE antibodies to pholcodine, used in cough suppressants in Norway but not in Sweden, were found in six per cent of blood donors from Norway but in none of the Swedish donors.
- Positive reactions to succinylcholine in 0.4 per cent and 3.7 per cent, of Norwegian blood donors and allergic subjects respectively. No serum from Sweden was positive.





# **NATIONAL PHOLCODINE CONSUMPTION AND PREVALENCE OF IGE-SENSITIZATION: A MULTICENTRE STUDY**

S. G. O. Johansson, E. Florvaag, H. man, L. K. Poulsen, P. M. Mertes, N. J. Harper, L. H. Garvey, R. Gerth van Wijk, T. Metso, A. Irgens, T. Dybendal, J. Halsey, A. B. Guttormsen, S. L. Seneviratne

**Allergy 2009 DOI: 10.1111/j.1398-9995.2009.02193.x**

Table 1. Accumulated PHO consumption in the nine participating countries and number of PHO-containing drugs on the individual national markets

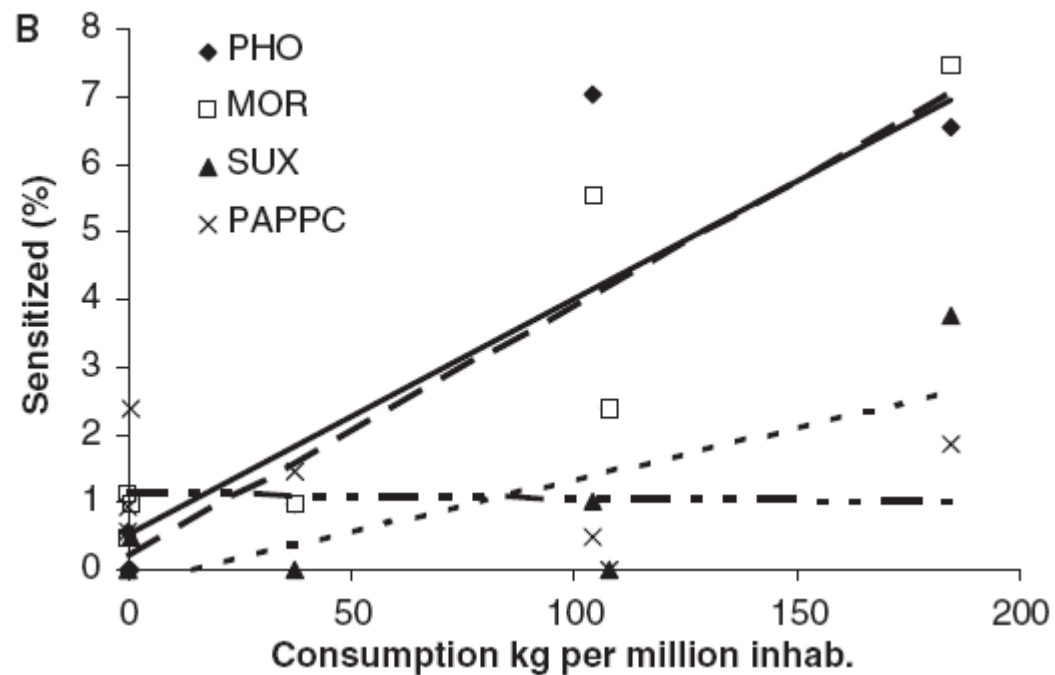
Country	PHO consumption (kg) during 2001–2005	PHO consumption kg per mill. inhab. during 2001–2005	No. of PHO-containing drugs on the market
Sweden	0	0	0
Denmark	0	0	0
USA	0	0	0
Germany	45	0.5	0
The Netherlands	163	10.1	0
Finland	195	37.5	1
Norway	470	104.4	1*
UK	6478	108.0	14
France	11095	184.9	14

\*Sera from Norway were collected before the drug was taken off the market in March 2007.

Table 2. Number of sera collected from the participating countries and the respective percentages of sera with IgE antibody levels of 0.35 kU<sub>A</sub>/l or higher to PHO, MOR, SUX and PAPPC


Country	City	No of sera	PHO %	SUX %	MOR %	PAPPC %
Sweden	Stockholm	213	0	0	0.5	0.9
Denmark	Copenhagen	179	0.6	0	1.1	0.6
USA	Lenexa	200	2.0	2.5	5.0	2.0
Germany	Freiburg	211	0	0.5	0.9	2.4
The Netherlands	Rotterdam	184	4.9	0	6.0	1.6
Finland	Helsinki	209	1.0	0	1.0	1.4
Norway	Bergen	199	7.0	1.0	5.5	0.5
UK	Manchester	209	2.4	0	2.4	0
France	Nancy	214	6.5	3.7	7.5	1.9





	Regression coefficient	$R^2$
PHO	0.037	0.767 ---
MOR	0.035	0.843 —
SUX	0.015	0.633 ····

Figure 2. Linear regression analysis of the associations between PHO consumption and IgE-sensitization to PHO, MOR, SUX and PAPPC in all countries (A), and after excluding NL and USA (B).



# Pholcodine (Tussokon<sup>®</sup>) in Sweden from 1970-1989

	<b>Reported anaphylaxis (per mill)</b>	<b>PHO consumpt (kg/mill)</b>	<b>PHO % pos</b>	<b>MOR % pos</b>	<b>SUX % pos</b>
<b>1970-1974</b>	<b>13 (1.6)</b>	<b>111 (13.5)</b>	<b>nt</b>	<b>nt</b>	<b>nt</b>
<b>1975-1979</b>	<b>24 (2.9)</b>	<b>77 (9.2)</b>			
<b>1980-1984</b>	<b>11 (1.3)</b>	<b>51 (6.1)</b>	<b>5.8</b>	<b>7.2</b>	<b>6.8</b>
<b>1985-1989</b>	<b>4 (0.5)</b>	<b>9.5 (1.1)</b>			
<b>1990-1994</b>	<b>0</b>	<b>0</b>	<b>0.9</b>	<b>1.8</b>	<b>0.9</b>
<b>1995-1999</b>	<b>0</b>	<b>0</b>			
<b>1999-2004</b>	<b>5 (0.6)</b>	<b>0</b>	<b>0</b>	<b>0.5</b>	<b>0</b>



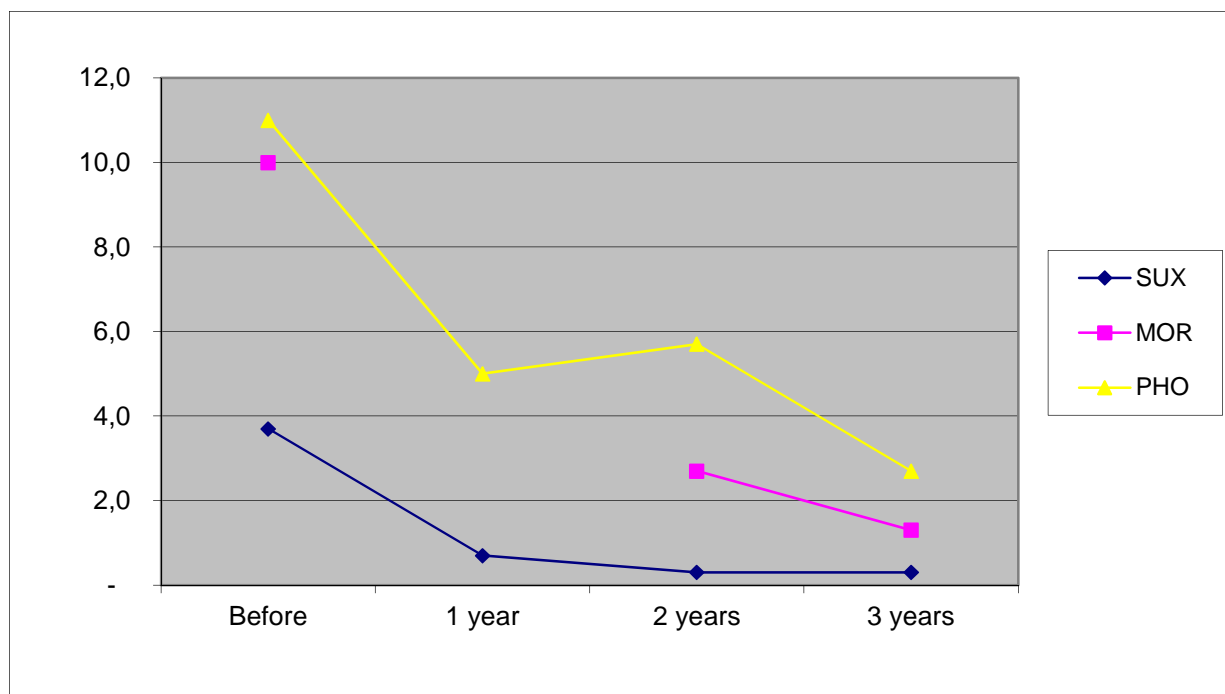
# 3 years follow-up study after withdrawal of pholcodine (Tuxi<sup>®</sup>)

**IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market.**

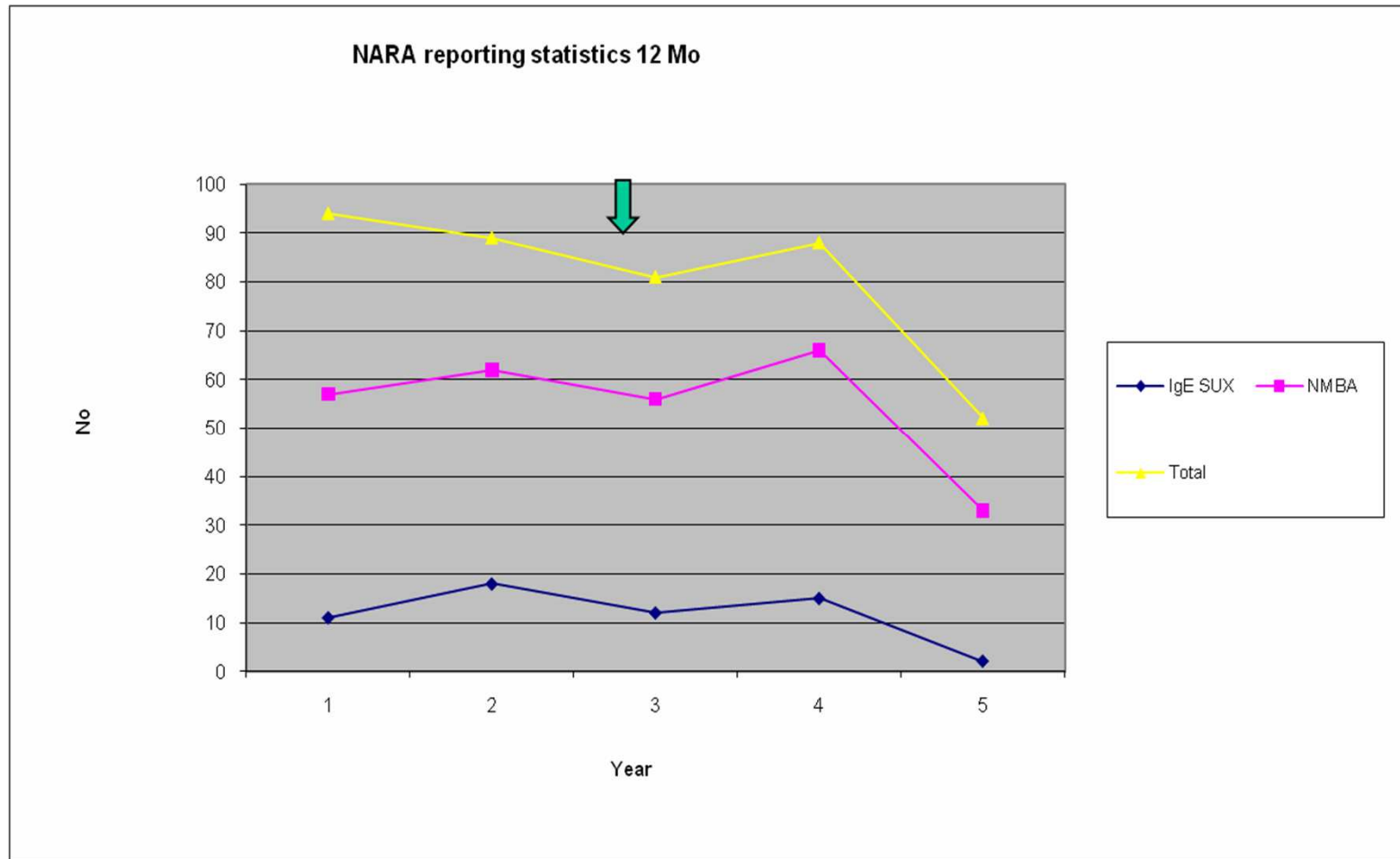
Florvaag E, Johansson SGO, Irgens Å, de Pater GH.  
Allergy 2011; **66**: 955-960.

# Prevalences of IgE sensitisation ( $\geq 0.35$ kUA/L) to PHO, MOR and SUX in 300 “allergics” after withdrawal

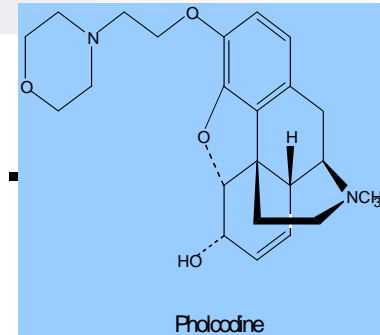
	Before	Years after Tuxi® withdrawal			Trend	P-value	P-value LbL
		1	2	3			
PHO	33 (11.0)	15 (5.0)	17 (5.7)	8 (2.7)	-0.418	<0.001	<0.001*
MOR	30 (10.0)	nt	8 (2.7)	4 (1.3)	-0.667	<0.001	<0.001*
SUX	11 (3.7)	2 (0.7)	1 (0.3)	1 (0.3)	0.002	0.002	<0.001*



# NARA reports on anaphylactic reactions during anaesthesia



# Conclusions at present .



## Pholcodine

- a small molecule key that turns on polyclonal IgE synthesis
  - by downregulating inhibitory mechanisms ?
- leads to IgE sensitization in a considerable proportion of exposed individuals
- has a striking effect on IgE synthesis in sensitized individuals
- can explain the differences in prevalence of IgE-sensitization and frequencies of reported NMBA anaphylaxis between Norway and Sweden
  - and possibly also for other countries



# The Pholcodine Hypothesis

- Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agent
- It has to be proved that pholcodine (or morphine and codeine) can act as sensitizing antigen
- The mechanism underlying the ‘immunological boosting’ effect exhibited by pholcodine remains unclear.



# RAP et exposition à la pholcodine?

- Aucune mention en 2009 ans la BNPV
- Plusieurs cas en 2012
  - Allergie à la pholcodine → tests curares +
  - Allergie à un curare → exposition pholcodine  
+
- Pholcodine listée depuis avril 2011.





## Tableau n°7 : Liste des 48 spécialités commercialisées en 2010 : Nom de spécialité Forme pharmaceutique

- attouxx adultes capsule
- attouxx toux sèche adultes sirop
- biocalyptol 6,55 sans sucre sirop
- biocalyptol à la pholcodine adulte suppo
- biocalyptol à la pholcodine enfant suppo
- biocalyptol à la pholcodine sirop
- Biocalyptol sirop
- broncalène adultes sans sucre sirop
- broncalène adultes sirop
- broncalène enfants sirop
- broncorinol adultes toux sèche pholcodine sirop
- clarix toux sèche pholcodine erysimum adulte édulcoré sirop
- clarix toux sèche pholcodine erysimum adulte sirop
- codotussyl adultes sol buv
- codotussyl adultes suppo
- codotussyl enfants suppo
- codotussyl toux sèche adulte sirop
- codotussyl toux sèche enfant sirop
- dénorol adulte sirop
- dénorol enfant sirop
- dimétane sans sucre sirop
- Ephedromel sirop
- hexapneumine adulte sirop
- hexapneumine adulte suppo
- hexapneumine enfant sirop
- hexapneumine enfant suppo
- humex adulte toux sèche pholcodine sirop
- humex enfant toux sèche pholcodine sirop
- myrtine enfant sirop
- pectoral richelet sans sucre sol buv
- pharmakod toux sèche sirop
- pholcodine delalande adulte sirop
- pholcodine winthrop adulte sirop
- pholcodyl sirop
- pholcones adulte suppo
- pholcones enfant suppo
- polery enfant sirop
- premidan adulte sirop
- premidan enfant sirop
- pulmadol enfant sirop
- pulmosodyl adulte sirop
- respilène adulte sirop
- respilène enfant sirop
- rhinathiol adulte toux sèche sirop
- rhinathiol enfant toux sèche sirop
- trophirès adulte sirop
- trophirès enfant sirop
- valda toux sèche sol buv

# 23 sirops à la pholcodine devront désormais être prescrits sur ordonnance

• 07/05/2011 à 09h38 • Catégorie: **évolution de la consommation**

## France

Afssaps - EMA


May 7th, 2011



23 sirops antitussifs à la pholcodine devront désormais **soumis à une prescription médicale obligatoire**. En effet, la pholcodine pourrait entraîner une sensibilisation aux curares accentuant ainsi les risques d'accidents allergiques lors d'anesthésies, selon l'Afssaps.

Sont ainsi concernés les sirops comme *Biocalyptol*, *Broncalène*, *Codotussyl toux sèche*, *Hexapneumine*, *Humex Pholcodine*, *Repsilène adultes*, *Rhinathiol Pholcodine*...

A la demande de la France, l'Agence européenne du médicament (EMA) procède actuellement à une **réévaluation du rapport bénéfice/risque** des médicaments contenant de la pholcodine.



# Perspective... étude ALPHO

- Réévaluation du rapport B/R de la pholcodine nov 2011
- Favorable
- Etude nécessaire
- « Est-ce que les patients exposés à la pholcodine ont un risque plus élevé de faire une réaction anaphylactique à un curare? »
- Etude cas-témoins



# ALPHO

- Cas : patients ayant présenté une réaction anaphylactique au cours de l'induction anesthésique
- Témoins: patients anesthésiés qui n'ont pas présenté de réaction anaphylactique (2 témoins/cas)
- Variable= exposition à la pholcodine
- Critères d'appariement des témoins:
  - Sexe
  - Âge (catégorie)
  - Région
  - Curare
  - Date+/- 20 jours



# Conclusion

- Importance des collaborations médecin généralistes-biologistes-allergologues-réanimateurs-pharmacovigilants
- Prévention sensibilisation: latex, pholcodine...



# Conclusion

- Une augmentation du nombre de cas notifiés
- Une réelle augmentation de l'incidence?
- Une augmentation de la sévérité
- Un facteur de sensibilisation? La pholcodine?
- Une étude en perspective: ALPHO
- Et la Xème enquête du GERAP est lancée!!!

Merci d'y Participer



*Merci*  
*de votre*  
*Attention*