POUR : Faut-il contre-indiquer les curares chez les patients sensibilisés à la pholcodine ?

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Conflits d’Intérêt

- Académique : GERAP, INSERM
- Conférencier : ALK, MSD
- ALPHO : Financement industriel par un consortium Zambon, Urgo, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bells Healthcare, Pinewood, T & R, Ernest Jackson:
Je soutiens la création du DES d’allergologie
## Estimated annual incidence of IgE-mediated allergic reactions during anesthesia

<table>
<thead>
<tr>
<th>Causal agents</th>
<th>Estimated annual number of case</th>
<th>Estimated annual incidence in France (/million)</th>
<th>Male</th>
<th>Overall</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>median [5th-95th perc]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMBAs</td>
<td>458 [326-590]</td>
<td>105.5 [79.7-132.0]</td>
<td></td>
<td>250.9 [189.8-312.9]</td>
<td></td>
</tr>
<tr>
<td>Latex</td>
<td>155 [110-200]</td>
<td>59.1 [44.8-73.6]</td>
<td></td>
<td>91.0 [68.9-113.4]</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>101 [72-131]</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Others agents</td>
<td>80 [57-103]</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*PM Mertes et al, JACI 2012*
Mortalité des RA

- 4,4% de 2000 à 2012
- 7% en 2012
- 6,4% en 2000...

**FACTEURS ASSOCIÉS À LA MORTALITÉ**

- Etude sur les 1931 cas survenus entre 2000 et 2011
- Analyse multivariée → facteurs de risque indépendants:
  - sexe masculin
  - contexte d’urgence
  - antécédent d’hypertension,
  - antécédent cardiovasculaire (autre que l’hypertension)
  - mention d’un bêtabloquant

*Reitter, Petitpain, Mertes, Allergy 2014*
NMBAs, allergy and immunological dogma
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.

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*
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.
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.
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
Origine de la sensibilisation aux curares?

- Génétique?
- Cosmétiques?
- Pholcodine?...
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.
Influence of occupationnal exposure in allergic reactions against muscle relaxants: The MIBAP study

**Design**
- A cohort study conducted in six vocational schools
- Follow-up, every six months after inclusion

**Population**
- Apprentices (2 year training) in bakery and hairdressing (quaternary ammonium compounds)

**Subjects**
- BHR determined by a metacholine challenge test (conducted at every visit, V1 to V4).
- Genetic polymorphisms
- Allergy occurrence

<table>
<thead>
<tr>
<th></th>
<th>Hair dressing</th>
<th>Pastry and bakery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.97 (1.69-14.66)</td>
<td>0.99 (0.20-4.95)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

The Pholcodine Hypothesis

Anaphylactic reactions to NMBAs are six times more common in Norway than in Sweden.

IgE to pholcodine, used in cough suppressants in Norway but not in Sweden, 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.

Florvaag et al, Allergy 2005: 60: 1312–1315
Morphiniques

Morphine

Codéine

Amine tertiaire (cyclique)

Groupement morpholinyl

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

Amines tertiaires (cycliques)
Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents

Pholcodine and guaifenesin, was administered at 10 ml once daily [one third of a therapeutic daily dosage] for seven consecutive days.

Allergy 2007: 62: 1445–14
National pholcodine consumption and prevalence of IgE-sensitization: a multicentre study

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

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

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

<table>
<thead>
<tr>
<th>Country</th>
<th>City</th>
<th>No of sera</th>
<th>PHO %</th>
<th>SUX %</th>
<th>MOR %</th>
<th>PAPPC %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>Stockholm</td>
<td>213</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Denmark</td>
<td>Copenhagen</td>
<td>179</td>
<td>0.6</td>
<td>0</td>
<td>1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>USA</td>
<td>Lenexa</td>
<td>200</td>
<td>2.0</td>
<td>2.5</td>
<td>5.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Germany</td>
<td>Freiburg</td>
<td>211</td>
<td>0</td>
<td>0.5</td>
<td>0.9</td>
<td>2.0</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Rotterdam</td>
<td>184</td>
<td>4.9</td>
<td>0</td>
<td>6.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Finland</td>
<td>Helsinki</td>
<td>209</td>
<td>1.0</td>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Norway</td>
<td>Bergen</td>
<td>199</td>
<td>7.0</td>
<td>1.0</td>
<td>5.5</td>
<td>0.5</td>
</tr>
<tr>
<td>UK</td>
<td>Manchester</td>
<td>209</td>
<td>2.4</td>
<td>0</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td>France</td>
<td>Nancy</td>
<td>214</td>
<td>6.5</td>
<td>3.7</td>
<td>7.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Pholcodine caused anaphylaxis in Sweden 30 years ago

Table 1. Reported cases of anaphylaxis during anaesthesia accumulated during the 10-year period, in parenthesis per million of inhabitants, average pholcodine (PHO) consumption, as Tussokon, in kg per year and, in parenthesis, per million and prevalence of IgE antibodies (> 0.35 kU\textsubscript{A}/l) to PHO, morphine (MOR) and suxamethonium (SUX)

<table>
<thead>
<tr>
<th></th>
<th>Reported anaphylaxis (per mill.)</th>
<th>PHO consumption (kg/mill.)</th>
<th>No. samples tested</th>
<th>PHO % pos</th>
<th>MOR % pos</th>
<th>SUX % pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970–1979</td>
<td>37 (4.5)</td>
<td>19.6 (2.4)</td>
<td>49</td>
<td>6.1</td>
<td>10.2</td>
<td>2.0</td>
</tr>
<tr>
<td>1980–1989</td>
<td>15 (1.8)</td>
<td>7.6 (0.9)</td>
<td>161</td>
<td>5.6</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>1990–1999</td>
<td>0</td>
<td>0</td>
<td>170</td>
<td>2.4</td>
<td>4.1</td>
<td>2.9</td>
</tr>
<tr>
<td>2002</td>
<td>0</td>
<td>0</td>
<td>300</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data from 2002 from Florvaag et al., 2005 (2).
Prevalences of IgE sensitisation ($\geq 0.35$ kUA/L) and reported cases of anaphylaxis to NMBAs after Pholcodine withdrawal

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Years after Tuxi® withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>PHO</td>
<td>33 (11.0)</td>
<td>15 (5.0)</td>
</tr>
<tr>
<td>MOR</td>
<td>30 (10.0)</td>
<td>nt</td>
</tr>
<tr>
<td>SUX</td>
<td>11 (3.7)</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

Allergy 2011; 66: 955–960
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 booster’ effect exhibited by pholcodine remains unclear.

- Pholcodine withdrawal led to decreased sensitization and reaction rates in Norway and Sweden

Ongoing Controversy

- Avoidance of cross-reacting NMBAs in patients allergic to pholcodine

- The negative predictive value of basophil activation tests might help to elucidate on the controversial putative cross-reactivity between pholcodine and NMBA
  Ley en et al, Cytometry Part B (Clinical Cytometry) 84B:65–70 (2013)
Sensitization to pholcodine and cross-reactivity to NMBAs

- Pholcodine:
  - 2 epitopes not recognized by specific IgE antibodies
  - 1 epitope common with curares
  - 1/3 to 1/10 of IgE directed against the ammonium quaternaire epitope

Katelaris et al, Asia Pac Allergy 2014; 4, 1
En Pratique à Strasbourg/ Recherche Clinique

- Allergie Pholcodine
  - Recherche de sensibilisation aux curares : tests cutanés, IgE (PAPPC ou SAQ) et CMF
  - Conseil fondé sur tests cutanés négatif (bonne valeur prédictive de CMF)

- Sensibilisation à la Pholcodine ? Pas d’exploration systématique en dehors de protocole de recherche
Anaphylaxie aux curares et exposition à la PHOLcodine
Recherche Biomédicale – Étude Cas-Témoins
Coordonnateur scientifique: Pr PM Mertes

Dès connaissance d’un  **CHOC ANAPHYLACTIQUE**
à l’induction anesthésique comprenant un curare
**TOUT ANESTHÉSISTE** est invité à composer sans tarder

📞 **Le 0 800 871 943 (n°vert)**

Pour permettre l’inclusion du patient dans l’étude
et la recherche de 2 témoins appariés par l’équipe de coordination de l’étude
Conclusions

- Hypothèse Environnementale Probable
- Hypothèse Pholcodine non démontrée mais des arguments
- En pratique : anesthésiste peu enclin à utiliser un curare positif en test cutané chez un sujet allergique à la pholcodine
- En attente des nouveaux résultats Norvégiens (manuscript en préparation)

- Un espoir

*Étude Alpho* : déclarez au numéro vert

0 800 871 943
Merci
Pour Votre
Attention
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
Methyl-substituted tertiary amine group