Patch Testing for Patients with Implants and Dental Amalgams: Critical Need to Standardize Patch Test Metal Allergens

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Founder of Contact Dermatitis Institute
SmartPractice:

- Pharmaceutical and medical device company committed to providing innovative and reliable solutions to help diagnose patients with allergic contact dermatitis and other conditions caused by Type IV hypersensitivity
- BLA holder for T.R.U.E. TEST
- Manufacturer of Finn Chambers®, AllergEAZE® Chambers, AllergEAZE® allergens
- Owner of SmartPractice Allergen Bank Compounding Pharmacy
Patch Testing for Patients with Implants and Dental Amalgams

- Type IV hypersensitivity to metals is among the etiologies known to contribute to implant failure and oral lichenoid reactions
- Diagnosis of Type IV hypersensitivity to metals in implantable devices may assist clinicians with information helpful in patient management
- The only standardized, FDA-approved metal patch test allergens are nickel, cobalt, chromium, gold included in T.R.U.E. TEST
- Successful diagnosis of Type IV hypersensitivity depends on use of standardized patch testing allergens, chambers, dispensed volumes, and test results interpretation
- Patch testing with Ni, Co, and Cr is a standard of care for many centers using the Nuss Bar (Obermeyer et al., 2018)

Reference:
Why is Standardization of Patch Test Metal Allergens Critically Important?

- Patch test results using non-standardized allergens are difficult to interpret and correlate with other evaluations.
- No standardized patch test metal allergens are available apart from those approved in T.R.U.E. TEST (nickel, cobalt, chromium, gold).
- Currently there are more than 20 different titanium compounds used for patch testing.
- Patch testing with titanium has been historically conducted with unstable or water-insoluble compounds that do not penetrate the stratum corneum.
- Use of vanadium and manganese salts with high irritation potential may result in irritant reactions erroneously interpreted as false positive reactions by inexperienced patch-testers.
- Published patch test results from case reports and small series of patients using dissimilar metal allergens at different doses/area with different excipients and chambers cannot be compared.
## Example: Ti Allergens

<table>
<thead>
<tr>
<th>Ti Compound</th>
<th>Chemical Formula</th>
<th>Molar Mass (g/mol)</th>
<th>% Ti (w/w)</th>
<th>Form</th>
<th>Solubility in Water and Stability in Air and Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titanium (metal)</td>
<td>Ti</td>
<td>47.9</td>
<td>100</td>
<td>Solid</td>
<td>Reacts slowly with air/water at ambient conditions, which inhibits further oxidation</td>
</tr>
<tr>
<td>Titanium(II)oxide</td>
<td>TiO</td>
<td>63.9</td>
<td>75</td>
<td>Solid</td>
<td>Unstable, and readily oxidizes in air</td>
</tr>
<tr>
<td>Titanium(III) oxide</td>
<td>Ti$_2$O$_3$</td>
<td>143.7</td>
<td>66.6</td>
<td>Solid</td>
<td>Unstable, and readily oxidizes in air to TiO$_2$</td>
</tr>
<tr>
<td>Titanium(IV) oxide</td>
<td>TiO$_2$</td>
<td>79.9</td>
<td>59.9</td>
<td>Solid</td>
<td>Stable, but insoluble in water</td>
</tr>
<tr>
<td>Titanium(III) nitride</td>
<td>TiN</td>
<td>61.9</td>
<td>77.4</td>
<td>Solid</td>
<td>Stable, but insoluble in water</td>
</tr>
<tr>
<td>Titanium(IV) carbide</td>
<td>TiC</td>
<td>59.9</td>
<td>79.9</td>
<td>Solid</td>
<td>Stable, but insoluble in water</td>
</tr>
<tr>
<td>Calcium titanate(IV)</td>
<td>CaTiO$_3$</td>
<td>135.9</td>
<td>35.2</td>
<td>Solid</td>
<td>Soluble in water but oxidizes to form a precipitate</td>
</tr>
<tr>
<td>Titanium(III) chloride</td>
<td>TiCl$_3$</td>
<td>154.2</td>
<td>31</td>
<td>Solid</td>
<td>Soluble in water but decomposes to TiO$_2$ &amp; HCl fume</td>
</tr>
<tr>
<td>Titanium(IV) chloride</td>
<td>TiCl$_4$</td>
<td>189.7</td>
<td>25.2</td>
<td>Liquid</td>
<td>Soluble in water but decomposes to TiO$_2$ &amp; HCl fume</td>
</tr>
<tr>
<td>Titanium(IV) sulfate</td>
<td>Ti(SO$_4$)$_2$</td>
<td>240</td>
<td>20</td>
<td>Solid</td>
<td>Soluble in water, but hydrolyzes</td>
</tr>
<tr>
<td>Titanium(IV) isopropoxide</td>
<td>TiC$<em>{12}$H$</em>{28}$O$_4$</td>
<td>284.2</td>
<td>16.8</td>
<td>Liquid</td>
<td>Rapidly decomposes in water to produce TiO$_2$</td>
</tr>
<tr>
<td>Titanium(III)oxalate (anhydrous)</td>
<td>Ti$_2$C$<em>6$O$</em>{12}$</td>
<td>359.8</td>
<td>26.6</td>
<td>Solid</td>
<td>Prone to oxidation in air, and sparingly soluble in water</td>
</tr>
<tr>
<td>Titanium(IV) oxalate (anhydrous)</td>
<td>TiC$_4$O$_8$</td>
<td>223.9</td>
<td>21.4</td>
<td>Solid</td>
<td>Stable, and very slightly soluble in water</td>
</tr>
<tr>
<td>Ammonium Titanium(IV) oxide</td>
<td>TiC$_4$H$_8$N$_2$O$_9$</td>
<td>276</td>
<td>17.3</td>
<td>Solid</td>
<td>Stable, and freely soluble in water</td>
</tr>
<tr>
<td>Potassium titanium(IV) oxide</td>
<td>TiC$_4$K$_2$O$_9$</td>
<td>318.1</td>
<td>15.1</td>
<td>Solid</td>
<td>Stable, and soluble in water</td>
</tr>
<tr>
<td>Ammonium titanium(IV) peroxo</td>
<td>Ti$<em>2$C$</em>{12}$H$_{24}$N$<em>4$O$</em>{18}$</td>
<td>608.1</td>
<td>15.7</td>
<td>Solid</td>
<td>Stable, and very soluble in water</td>
</tr>
<tr>
<td>citrate (anhydrous)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titanium(IV) lactate ammonium</td>
<td>TiC$<em>6$H$</em>{18}$N$_2$O$_8$</td>
<td>294.1</td>
<td>16.3</td>
<td>Liquid</td>
<td>Stable as a clear aqueous solution (approx. 50%)</td>
</tr>
<tr>
<td>hydroxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titanium(IV) lactate</td>
<td>TiC$<em>{14}$H$</em>{34}$N$_2$O$_8$</td>
<td>406.3</td>
<td>11.8</td>
<td>Solid</td>
<td>Stable as a pearly white aqueous solution (approx. 40%)</td>
</tr>
<tr>
<td>tetramethylammonium hydroxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titanium peroxide</td>
<td>H$_4$O$_4$Ti</td>
<td>115.9</td>
<td>41.3</td>
<td>Solid</td>
<td>Stable but insoluble in water</td>
</tr>
<tr>
<td>Titanium salicylate</td>
<td>C$<em>{28}$H$</em>{20}$O$_{12}$Ti</td>
<td>596.3</td>
<td>8.0</td>
<td>Solid</td>
<td>Stable, and slightly soluble in water</td>
</tr>
<tr>
<td>Titanium tannate</td>
<td>Ti(C$<em>{76}$H$</em>{48}$O$_{46}$)$_4$</td>
<td>174.5</td>
<td>2.7</td>
<td>Solid</td>
<td>Stable, but insoluble in water</td>
</tr>
</tbody>
</table>

Example: Insoluble vs Soluble Titanium

Crystalline Structure

Insoluble: Ti dioxide

Soluble: Ti Oxalate Dihydrate

Source:
Approach for Development of Standardized Metal Patch Test Allergens

- Need for rigorous investigation to provide consistent data similar to those collected for registration of T.R.U.E. TEST
- Selection of metal allergen salts for clinical trial based on:
  - Chemical stability in air, water, transport temperatures, petrolatum, and hydrogels
  - Water solubility
  - Optimized pH
  - Skin penetration potential
- Use of robust and validated methods for quality control and stability of metal allergens compliant with FDA and ICH guidances
- Selection of standard dose based on data from a dose response clinical trial on subsets of subjects with clinical history of symptoms consistent with the metal Type IV hypersensitivity
- Demonstration of efficacy and safety in a Phase 3 study
Phase 2 Dose Response Studies for Metal Allergens

- SmartPractice has completed two Phase 2 dose response studies
- Investigation included:
  - 17 different salts for total of 10 metal allergens
  - For each salt, a series of 3 to 5 doses
  - 8 clinical sites in the USA, Europe, and Japan
- Clinical responses were generally proportional to dose/area
- Selection of the optimal salt/dose was based on:
  - Number and frequency of 1+ and 2+ positive reactions
  - Frequency of sustained reactions
  - Frequency of strong (3+) and/or late reactions (fewer preferred)
  - Frequency of doubtful and irritant reactions (fewer preferred)
  - Concordance with petrolatum allergen comparator
- Mercury did not meet the Phase 2 endpoints; there were challenges with discordant results in patients with past positive patch test reactions; and mercury allergens are not stable at room temperature
Phase 3 Safety and Efficacy Study for Metal Allergens

- Seven (7) metal allergens have been selected for further investigation in the Phase 3 Study:
  - Titanium
  - Vanadium
  - Manganese
  - Palladium
  - Zinc
  - Tin
  - Copper

- Next step: conducting a Phase 3 efficacy and safety study for the new panel registration

- During investigation, these 7 metal allergens are available on a patient prescription basis through “SmartPractice Allergen Bank” compounding pharmacy
Thank you!

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