Drug Desensitization

Anne Liu, MD
Stanford University School of Medicine
Faculty Disclosure for
Anne Liu, MD

For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

- Honoraria received from: None
- Consulted for: None
- Held Common Stock in: None
- Research, clinical trial, or drug study funds received from: None

I will not be discussing products that are investigational or not labeled for use under discussion.
Overview

- Desensitization basics
- Patient selection
- Rapid desensitization
  - Protocol
  - Premedication
  - Treating reactions
  - Antibiotics
  - Chemotherapy
  - Monoclonal antibodies
  - Mechanism
- Slow desensitization
  - Protocols
1928
SUCCESSFUL DESENSITIZATION IN PENICILLIN SENSITIVITY

SAMUEL M. PECK, M.D.
and
SHEPPARD SIEGAL, M.D.
With the assistance of
ROSE BERGAMINI, B.A.
New York

Penicillin is finding increasingly wide use in present day medical practice. The clinical indications for its use were at times of many or, at other times of less severity, the patient was not well. The result, however, was the same: the fever, absence of appetite, and other symptoms of the disease were relieved. The patient became strong, was able to eat and to ambulate. In many instances, penicillin has been used because it is the only agent available which can attack the causative agent of the disease. The patient was discharged from the hospital with a promise that he would return in a few days for further observation. The patient was discharged and returned to his home. He was taken care of by the local physician, and was discharged from the hospital.

On the fourth day only three injections totaling 90,000 units could be given, because the patient developed an acute erythematovesicular eruption on the hands, feet and groin. The eruption rapidly spread to involve the entire body. The skin on the body showed a scarlatiniform type of eruption with edema of the face. There were some vesicles on the forearms. The eruption gradually subsided, but desquamation of the hands and feet was still evident one month later. There
Drug Desensitization Basics

- Incremental dose administration of a drug over hours or days
- Abrogates immediate and delayed HSR
- History of HSR:
  - IgE mediated
  - Non-IgE mediated with immediate features
  - Delayed type HSR
Drug Desensitization Basics

- Desensitization is a temporary state
- Lasts as long as drug is in circulation (2-3 half lives)
- Subsequent administrations must be by desensitization
- Redesensitization is required if doses are missed
Desensitization protocols

- Antibiotics
- Biologics / Monoclonals
- Chemotherapy
- Antiretrovirals, antimycobacterials
- ASA
- Iron
- Progesterone
- Allopurinol
- Insulin
- Vaccines
Desensitization protocols

- Antibiotics
- Biologics / Monoclonals
- Chemotherapy
- Antiretrovirals, antimycobacterials
- ASA
- Iron
- Progesterone
- Allopurinol
- Insulin
- Vaccines
Candidate selection

- Reaction characteristics
  - Immediate vs delayed
  - Severity
- Patient characteristics
  - Comorbidities
  - Ability to report/monitor symptoms
  - Ability to follow up
- Skin testing
- Indication for medication
Rapid desensitization: process

- Inpatient (first time in ICU)
- Allergy consultation
- Monitored setting where intubation and resuscitation can be performed easily
- 1:1 nursing ratio
- Rescue medications immediately available
- Reactions are not always predicted by prior desensitization
Rapid desensitization protocols

- Many protocols published.
- BWH experience with a 3-4 concentration protocol, with doubling doses/rates every 15-30 minutes.
- For chemotherapy, antibiotics, monoclonals, iron.

Castells 2008
Brennan 2009
Legere 2009
Sample protocol

### TABLE I. Desensitization protocol for intravenous infliximab (600 mg)

<table>
<thead>
<tr>
<th>Step</th>
<th>Solution</th>
<th>Rate (mL/h)</th>
<th>Time (min)</th>
<th>Volume infused per step (mL)</th>
<th>Dose administered with this step (mg)</th>
<th>Cumulative dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2.0</td>
<td>15</td>
<td>0.50</td>
<td>0.012</td>
<td>0.012</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5.0</td>
<td>15</td>
<td>1.25</td>
<td>0.030</td>
<td>0.042</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>10.0</td>
<td>15</td>
<td>2.50</td>
<td>0.060</td>
<td>0.102</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>20.0</td>
<td>15</td>
<td>5.00</td>
<td>0.120</td>
<td>0.222</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>5.0</td>
<td>15</td>
<td>1.25</td>
<td>0.300</td>
<td>0.522</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>10.0</td>
<td>15</td>
<td>2.50</td>
<td>0.600</td>
<td>1.122</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>20.0</td>
<td>15</td>
<td>5.00</td>
<td>1.200</td>
<td>2.322</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>40.0</td>
<td>15</td>
<td>10.00</td>
<td>2.400</td>
<td>4.722</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>10.0</td>
<td>15</td>
<td>2.50</td>
<td>5.953</td>
<td>10.675</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>20.0</td>
<td>15</td>
<td>5.00</td>
<td>11.906</td>
<td>22.580</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>40.0</td>
<td>15</td>
<td>10.00</td>
<td>23.811</td>
<td>46.392</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>80.0</td>
<td>174.38</td>
<td>232.50</td>
<td>553.609</td>
<td>600.000</td>
</tr>
</tbody>
</table>

Total time = 340 min (5.66 h)

Solution 1, 0.024 mg/mL; solution 2, 0.24 mg/mL; solution 3, 2.38 mg/mL.

Brennan 2009
Premedication

- H1 antagonist?
- H2 antagonist
- +/- ASA
- +/- Montelukast
- Avoid steroids
- Hold beta blockers if possible

Breslow 2009
Rescue medications

- H1 antagonists
- H2 antagonists
- Epinephrine (+/- glucagon)
- Albuterol, ipratropium
- Role of steroids
- ASA
- Leukotriene antagonists
- Anxiolytics
- Role of methylene blue?
Treating reactions

- Take careful note of details of reaction (VS, symptoms, duration, medications required for resolutions, protocol step)
- Pause protocol, treat to resolution, resume.
  - Usually can resume rate at which infusion was paused.
Adjunctive medications

- Post medications
- Anticipatory modifications for patient’s subsequent desensitization:
  - Prolonging step prior to anticipated
  - Add intermediate rate step
  - Premed at specific step
Antibiotic desensitization

- Extensive experience of repeated desensitizations in cystic fibrosis patients
- Target concentration should be the standard concentration for that antibiotic, since completion of course will occur at that concentration.

Legere 2009
Antibiotic desensitization

- If there are alternatives, why still pursue desensitization?
  - Inferior efficacy
  - Higher cost
  - Development of resistance
  - Greater toxicities
Chemotherapy: skin testing

- Carboplatin skin test: false negative rate ~8% (false positive rate unknown)
  - 30% carboplatin-allergic patients are cross-sensitized to cisplatin.
- Cyclophosphamide, MTX
- Taxane skin testing: not predictive
- Do not ST using known vesicants (e.g., doxorubicin).

Markman 2003
Lee 2005
Weiss 1990
Chemotherapy desensitization

- 413 chemotherapy desensitizations.
  - 94% mild/no reaction.
  - 6% severe reactions
  - All successfully received tx.
  - Reactions were more mild than the original reaction.
- Reactions tend to occur after interval without chemotherapy.

Castells 2008
Monoclonal antibody reactions

- Large MW, act as complete Ag
- Targeted by both T and B cells
- On-target effects, usu. surface receptors
- Long half-lives, dosing intervals
- Humanized versions may be an alternative.
- Fevers, rigors, myalgias
- Majority of reactions occur on first administration
Desensitization to mAb

- Patient selection challenges
- ST can be helpful

Brennan 2009
Proposed mechanisms for rapid desensitization

- Gradual cross-linking of drug-specific IgE on mast cells, < threshold
- Rapid internalization cross-linked FcεRI receptors
- Excess monomeric Ag incapable of cross-linking surface FcεRI receptors
- IgE induced loss of Syk kinase
- STAT6 involvement?
- Not well understood

Solensky 2004
Chisholm-Burns 2007
Macglashan 2004
Morales 2005
Slow desensitization

- Benign delayed type hypersensitivities
- Careful patient selection
- Compounding pharmacies
- Established protocols:
  - Trimethoprim/sulfamethoxazole
  - Allopurinol
  - Some anti-mycobacterials, anti-retrovirals
Slow desensitization

- Many protocols described in literature
- Vary by starting dose, number of steps, number of days.
- Little data comparing different protocols
- Fluconazole, rifampin, isoniazid, acyclovir
- Unknown mechanism
- Role of skin and patch testing unknown
Challenges of desensitization

- Labor and resource intensive
- Requires close and continuous monitoring
- Variability in administration
- Idiosyncratic reactions can mimic immediate type HSR
- Slow oral desensitizations have variable success rates
Future questions

- Role of omalizumab in drug desensitization
- Predictors of successful and continued desensitization
- Special populations:
  - Organ transplant
  - Neutropenic, chemotherapy
  - ICU patients: low sensitivity of skin testing
- Other types of hypersensitivity reactions?
References