Navigating the World of Adverse Drug Reactions

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Adverse Drug Reactions

Upon completion of this activity, the participant should be able to:
• Understand how to categorize various adverse medication effects.
• Demonstrate the ability to take a thorough history of a medication intolerance episode.
• Summarize the management of medication intolerance, based on a thorough history.

Definition

• Adverse Drug Reactions:
  – “Any noxious, unintended and undesired effect of a drug that occurs at doses used for prevention, diagnosis or treatment.”
  – World Health Organization

Overview: Adverse Drug Reactions (ADRs)

• Case illustrating history-taking skills
• Breaking down ADRs
• Skin manifestations
• Common ADRs in Clinical Practice
• Summary

Essential History Taking

• Medication name?
• How long ago did reaction occur?
• Which organ systems were involved?
• When during the course did the reaction occur?
• Why was the medication prescribed?
• What other meds were being taken?

Essential History Taking

• What was the therapeutic management taken secondary to the reaction?
• Has the patient experienced similar reactions in the absence of drug therapy?
• Has the patient experienced a similar reaction to the same or similar medication?
• Does the patient have an underlying condition that predisposes to the reaction?
Case

- Mr. Hyper Tension is a 50 year old man who was found to have serial high BP recordings, usually around 150/90. He was started on lisinopril 10 mg daily. One week later his blood pressure was 110/70 and he (and his potassium) were tolerating the lisinopril well.

- Two months later, he calls back complaining of a dry cough for the past month. He denies fever or cold symptoms. He stopped the lisinopril 3 days ago, because he thought it had triggered the cough.

- Other medications include aspirin, simvastatin and MVI.

Essential History Taking

- Medication name? Lisinopril
- How long ago did reaction occur? 1 month
- Which organ systems were involved? Respiratory
- When during the course did the reaction occur? One month after starting
- Why was the medication prescribed? High BP
- What other meds were being taken? Aspirin, simvastatin, MVI.

Essential History Taking

- What was the therapeutic management taken secondary to the reaction? Patient stopped taking
- Has the patient experienced similar reactions in the absence of drug therapy? No
- Has the patient experienced a similar reaction to the same or similar medication? No
- Does the patient have an underlying condition that predisposes to the reaction? Don’t know

Unpredictable ADRs

- 20% of all ADRs
- Susceptible subjects
- Dose-independent, non-pharmacologic
- Examples:
  - Drug intolerance (tinnitus after taking one aspirin)
  - Drug idiosyncrasy (G6PD deficiency: anemia after taking hydroxychloroquine)
  - Drug allergy (Anaphylaxis after penicillin)
  - Pseudoallergic reactions (Hives after taking morphine)

Predictable ADRs

- 80% of all ADRs
- Healthy subjects
- Dose-dependent, Pharmacologic
- Examples:
  - Overdose (acetaminophen and hepatic failure)
  - Side effects (tremulousness with albuterol)
  - Secondary effects (bacterial overgrowth after antibiotics)
  - Drug interaction (one drug affecting another drug’s metabolism)

Unpredictable ADRs

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Table 1. Heterogeneity of drug-induced allergic reactions (continued)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Anaphylaxis</td>
<td>Betaxolol, methyldopa, propranolol</td>
<td>Penicillin, cephalosporins, sulphonamides</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Penicillins, kedua, propylthiouracil</td>
<td>Phenobarbital, aciclovir, phenothiazines</td>
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<tr>
<td>Urticaria</td>
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<td>(</td>
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<tr>
<td>Fixed Drug Eruptions</td>
<td>Amoxicillin, sulphonamides</td>
<td>Penicillin, sulphonamides, gold, procainamide, allopurinol</td>
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<td>Stevens-Johnson Syndrome</td>
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**Beta Lactam Antibiotic Allergy**

- Penicillin is still the drug of choice for:
  - Group A-hemolytic streptococcal pharyngitis
  - Certain subtypes of endocarditis
  - Tertiary syphilis in pregnancy
- Carbapenems (doripenem, imipenem, ertapenem, meropenem) share β-lactam ring, but >99% of PCN skin test POSITIVE patients... can be given a carbapenem without a reaction.
- The monobactam aztreonam can be given to penicillin-allergic patient without testing.

**Cephalosporins and penicillins with common side chains**

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Amoxicillin</th>
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<tbody>
<tr>
<td>Cefadroxil</td>
<td>Cefaclor</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>Cephalexin</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Cephradine</td>
</tr>
<tr>
<td>Cephaloglycin</td>
<td>Loracarbef</td>
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<tr>
<td>(carbecepham)</td>
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</tbody>
</table>

List of cephalosporins that share identical R1-group side chains with R-group side chain of amoxicillin and ampicillin.

**Beta Lactam Antibiotic Allergy**

- Of all patients reporting a history of PCN allergy, 85-90% will tolerate PCN
  - Allergy has been lost
  - Misdiagnosis ("my grandmother was allergic, so I was told I was allergic")
- Among PCN skin test positive patients, approximately 2% will react to a cephalosporin
- Penicillin is the only antibiotic for which there is standardized skin testing available
- Penicillin can participate in all 4 of the classic Gel & Coombs reactions!
Aspirin Exacerbated Respiratory Disease

- Max Samter, MD
  - U of I, Chicago
  - ENT
- Samter’s Triad
  - Asthma
  - Aspirin sensitivity
  - Nasal polyposis

Aspirin Sensitive Asthma

- ASA sensitive most common, ages 20-40
- Females with slightly greater incidence in Scripps series (58% vs. 42%, N=300)¹.
- Giraldo² noted 5% incidence of a past history of ASA-induced respiratory reactions in hospitalized, adult asthmatics
- 1972 Scripps study³, oral challenge in adult asthmatic patients
  - Found 9% to be ASA sensitive
  - 30-40% prevalence if also carried history of rhinitis OR nasal polyps

Angiotensin Converting Enzyme Inhibitors - Cough

- Incidence 5-20%
- Onset - one week to six months
- Mechanism – Bradykinin or Substance P (both normally metabolized by ACE)
  - increase, inducing prostaglandin E2 accumulation and vagal stimulation.
  - Angiotensin II receptor blockers do not cause cough
  - 4 weeks off of ACE inhibitor is sufficient to make the diagnosis

Angiotensin Converting Enzyme Inhibitors - Angioedema

- African Americans, smokers at higher risk
- Face, lips and tongue, classically
- 0.1-0.7% incidence
  - Highest incidence during 1st month of treatment
  - 27% may occur greater than 6 months after starting therapy
  - Inhibiting ACE leads to unopposed bradykinin formation, causing angioedema

Angiotensin Converting Enzyme Inhibitors - Angioedema

- Patients with a history of angioedema may develop angioedema during ACE inhibitor therapy.
- Management includes discontinuation of the ACE inhibitor and treatment with corticosteroids or other antihistamines.

¹McDonald et al 1972;²Giraldo et al 1969
### Vaccines: Points to Consider

- Mild local reactions and/or constitutional symptoms following vaccine administration are not contraindications for future use
- Anaphylaxis to vaccines is rare (1 in a million, out of 235 million vaccines per year)
- Report adverse events (Vaccine Adverse Events Reporting System, VAERS)
- Fatalities exceedingly rare

### Vaccines

- Td toxoid
  - Local reactions common
- MMR
  - Gelatin allergy is an issue, not egg (do not need to test for egg – chick fibroblast culture)
- Rabies vaccine – chick fibroblast culture
- Influenza
  - Egg allergy is listed as contraindication for flu shot
  - But, the vast majority of patients with egg allergy can safely receive flu shot
  - Guillain Barre Syndrome, rarely
- Yellow fever
  - Contains egg and gelatin
- Japanese encephalitis
  - Gelatin (anaphylaxis has been reported)

### Multiple Drug Allergy Syndrome

- Familial tendency for immunologic drug reactions
  - Having just one parent with an antibiotic allergy makes one 15 times more likely to carry a drug sensitivity, by history
- Penicillin reactors have higher incidence of other drug allergies
- Vast array of clinical reactions are possible
- Mechanism is likely that of enhanced immunogenicity to drugs that are more apt to haptenate
  - Can be IgE or non-IgE in origin

### Anaphylactoid Reactions

- No IgE Involvement (no testing available)
- Involve same final common pathway as type I, IgE-mediated reaction
- Three examples:
  - Contrast dye used in computed tomography
    - Premedication regimen available
  - Opiate-induced urticaria
  - Aspirin-induced asthma (AERD)

### Dentist’s Office

- True, IgE-mediated anaphylaxis to local anesthetics is extraordinarily rare!
- Adverse effects of anesthetics/vasoconstrictor combinations include:
  - Vasovagal syncope
  - Paresthesias, lightheadedness (“caines”)
  - Palpitations, anxiety (epinephrine)
- General anxiety/panic

### Reporting Adverse Reactions to MedWatch

- Internet
  - [www.fda.gov/medwatch](http://www.fda.gov/medwatch)
- Phone
  - 1 800 FDA 1088 (general line)
  - 1 800 FDA 0178 (to fax report)
  - 1 800 FDA 7967 (for Vaccine Adverse Event Reporting System (VAERS))
Summary

• Adverse drug reactions are a component in a substantial numbers of patients utilizing any type of pharmacotherapy
• A complete history is the most useful tool to assess whether certain symptoms are due to ADRs
• Standardized skin testing for Type 1 hypersensitivity is only available for penicillin at this time