Uncommon, Unexpected, and Eccentric Adverse Drug Reactions

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Disclosure

• I have nothing to disclose at this time

Objectives

By the end of the presentation, you should be able to:

1) Describe the pathophysiology of uncommon adverse drug reactions
2) Identify appropriate counseling points and monitoring parameters for uncommon adverse drug reactions
3) Describe treatment of rare and uncommon adverse drug reactions

Is There a “Perfectly Safe” Medication?

Inspiration

• Real life experiences
  • “I heard that…”
  • Music
  • Words of Wisdom

“TDF” Think Drugs First

DRUGS ARE BAD
First, a Step Back

- What is an ADR?
  - “Directly caused by drug at normal doses and normal use”
  - “Likely involves causal link between drug and reaction”
- What is an ADE?
  - “Injury resulting from use of a drug”
  - “Includes ADR, overdoses, dose changes, discontinuing drugs”

Just to Clarify

- Allergy – ADR mediated by immune response
- Side-Effect - An expected and known effect of a drug that is not the intended therapeutic outcome

ADR Classification

MILD:
Minimal therapeutic intervention

MODERATE:
Requires active treatment or further testing or evaluation

SEVERE:
- Any serious outcome resulting in life or organ threatening situation or death
- Significant/permanent disability, requiring intervention or prolonging hospital stay

Identifying ADR’s

- Clinical Trials
  - Identify common ADR’s
- Limitations
  - Size
  - Duration
  - Exclusion criteria
### ADR Frequency

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>Common (frequent)</td>
<td>≥1/100 and &lt; 1/10</td>
</tr>
<tr>
<td>Uncommon (infrequent)</td>
<td>≥1/1000 and &lt; 1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10000 and &lt; 1/1000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 1/10000</td>
</tr>
</tbody>
</table>

### Why Care about ADR’s?

- We are Pharmacists
- Drugs are what we **DO**
- ADR’s are expensive
- Most importantly:
  - Patient safety

### Nitroprusside

- **Class:** Direct Vasodilator
- **Indication:**
  - BP reduction in HTN Crisis
  - Controlled hypotension
  - Acute CHF
- **MOA:** Relaxation of vascular smooth muscle and dilation of peripheral arteries and veins

### Nitroprusside Cyanide Toxicity

Exposure to Hemoglobin

4 of 5 cyanide ions released

Remaining cyanide ion combines with methemoglobin to form cyanmethemoglobin
What about the other 4 cyanide ions?

Transulfuration
- Thiosulfate donates sulfhydryl group
- Combines with cyanide
- Forms Thiocyanate
  - Excreted by kidneys

Thiosulfate
- Average adult can detoxify 50mg of nitroprusside
- Once depleted:
  - Cyanide levels rise in blood
  - Toxicity

Nitroprusside Cyanide Toxicity
- If more than 500 μg/kg given faster than 2 μg/kg/min
  - Cyanide generated

Nitroprusside Cyanide Toxicity
- Antidote:
  - Sodium thiosulfate
  - Co-infusions:
    - Give at rates of 5-10 times that of sodium nitroprusside.

Nitroprusside Cyanide Toxicity
- How rare?
  - 52 cases reported between 1974 and 1992
  - Recent review
    - 1.87% incidence
    - 0.6% mortality rate
Nitroprusside

What would be an appropriate method to prevent cyanide toxicity secondary to nitroprusside administration?
A. Limit dose to 2 μg/kg/min if total dose is greater than 500 μg/kg
B. Limit dose to 4 μg/kg/min if total dose is greater than 500 μg/kg
C. Utilize a co-infusion of sodium thiosulfate
D. Administer with a normal saline bolus of 500mL
E. A and C

Phentermine

• Case Report of Rhabdomyolysis
  • 32 year old male
    • PMH significant for drug abuse, LSD, EtOH and cocaine
    • “Strenuous Activity”
    • Recent change started phentermine 37.5mg BID
    • Naranjo scale of 5 (probable)

Phentermine

• Class: Anorexiant; Central Nervous System Stimulant; Sympathomimetic
• Indication: Short term weight loss treatment
• MOA: Sympathomimetic amine similar to amphetamine

Phentermine

• Common Side Effects:
  • Xerostomia
  • Insomnia
  • Irritability

Phentermine vs. Amphetamines

• Causation?
Controversy

Rhabdomyolysis and phentermine: Coincidence, not causation

The case report by Frölt et al. described a 26-year-old man who developed rhabdomyolysis, "related to excessive use of phentermine hydrochloride." Significantly, the patient had engaged in recreational use of rhabdomyolysis-inducing substances. In their discussion, Frölt et al. reiterated the common misconception that all recreational substances heighten pharmacokinetic properties and adverse effects. On the con.

The Unexpected

Musical Interlude

“I’m allergic to doc prescribed antihistamines”

‘Welcome to Atlanta’
Ludacris ft. Jermaine Dupri
Released April 2002

16 year old non-pharmacist
Cory:
“That doesn’t make sense!”

Cetirizine

• Class: Second Generation Antihistamine
• Indications:
  • Perennial and seasonal allergic rhinitis
  • Urticaria
• MOA
  • H₁ receptor antagonist

How would you counsel a patient taking cetirizine?

• Indications
• Dosing
• Potential Side Effects?
Cetirizine

- Common Side Effects:
  - >10%
  - Headache, somnolence
  - 2-10
  - Insomnia, malaise, fatigue, dizziness, abdominal pain, dry mouth

Urticarial Reaction

Patient Case

- 29 YOF with 2 year hx of urticaria
- Diagnosis
  - “chronic idiopathic urticaria.”
  - Treated with cetirizine 20mg/day

Patient Case

- Admitted for diagnostic purposes
  - Cetirizine stopped
- Urticaria resolved after 4 days
  - Re-challenged 7 weeks later

What do we think happened?

Cetirizine

- Rare instances of urticarial type of response
  - Suggest non-immunological
  - “Non Allergic” Hypersensitivity
  - Lack of IgE response

TIMEOUT

Immunology/Dermatology Lesson
Immunology: Remember this?

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Primary Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>Neutralizing Antibody</td>
</tr>
<tr>
<td>IgD</td>
<td>B Cell Activation</td>
</tr>
<tr>
<td>IgE</td>
<td>Allergic reactions, Parasitic Infections, Hypersensitivity Reactions</td>
</tr>
<tr>
<td>IgG</td>
<td>Humoral Response, Activates Complement System, Phagocytosis</td>
</tr>
<tr>
<td>IgM</td>
<td>Agglutination and cytolytic reactions</td>
</tr>
</tbody>
</table>

Antibody Types

Immunology Time-Out

- Type I-immediate/anaphylactic
  - Mediated by IgE
- Type II-cytotoxic
  - IgM/IgG
- Type III-Immune Complex Hypersensitivity
  - IgM/IgG
- Type IV-cell mediated/delayed
  - Autoimmune/Infectious Diseases

Dermatology

- Urticaria: “batches of raised, red or white itchy welts (wheals)“

More Simply Put:

HIVES

Cetirizine

- Rare instances of urticarial type of response
  - Suggest non-immunological
  - “Non Allergic” Hypersensitivity
  - Lack of IgE response

Cetirizine-What to Look For

- Urticaria
- Maculopapular lesions
- Chronic urticaria not relieved
  - Despite treatment with cetirizine
  - Rarely anaphylaxis
Lisinopril

- Class: Angiotensin Converting Enzyme Inhibitor
- Indications: Hypertension, Heart Failure, Nephropathy
- MOA: Prevents conversion of angiotensin I to angiotensin II

Clinical Scenario

A patient with hypertension is started on your favorite ACE inhibitor

How would you monitor?

- Efficacy
- Safety
- Labs

Common Lab Abnormalities

- Hyperkalemia
- Increased serum creatinine

How many of you would be concerned about sodium?

ACE Inhibitor Induced Hyponatremia

- 49 Year old male
  - Referred to pharmacy managed HTN clinic
  - Lisinopril added to HTN regimen
  - Developed hyponatremia

Real Life!

How many of you would be concerned about sodium?

49 Year old male
- Referred to pharmacy managed HTN clinic
- Lisinopril added to HTN regimen
- Developed hyponatremia

<table>
<thead>
<tr>
<th>Date</th>
<th>BP</th>
<th>Drug Tx</th>
<th>Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/13/13</td>
<td>149/101</td>
<td>Atenolol 25mg daily HCTZ 25mg daily Added lisinopril 20mg daily</td>
<td>136</td>
</tr>
<tr>
<td>7/11/13</td>
<td>-</td>
<td>Pi STOPPED HCTZ/Lisinopril 25/20mg Changed to HCTZ 25mg daily Atenolol 25mg daily</td>
<td>130</td>
</tr>
<tr>
<td>7/16/13</td>
<td>136/84</td>
<td>HCTZ 25mg daily Atenolol 25mg daily Increased to 50mg daily</td>
<td>134</td>
</tr>
<tr>
<td>8/8/13</td>
<td>-</td>
<td>Atenolol 50mg daily HCTZ 25mg daily</td>
<td>139</td>
</tr>
<tr>
<td>8/29/13</td>
<td>120/71</td>
<td>Atenolol 50mg daily HCTZ 25mg daily</td>
<td></td>
</tr>
</tbody>
</table>
Lisinopril Induced Hyponatremia

- Case reports in literature
- Multiple agents
- Various Outcomes
  - Drug discontinuation
  - Seizures
  - Death

How would you monitor a patient newly started on Lisinopril?

RAAS System

Lisinopril and Hyponatremia

- Hyponatremia
  - Rare but possible
  - Monitor renal panel
  - Assess for risk factors:
    - EtOH
    - Other medications
    - Polydypsia

Proposed Mechanism

- Not completely understood
- Possible SIADH
- Multiple ACE inhibitors implicated

Hydroxychloroquine

- Class: Anti-Inflammatory, Antimalarial
  Indication: Lupus, Malaria, RA
- MOA: exact unknown
- Common Side Effects: Blurred Vision, GI, HA, anorexia, skin rash/pruritis
Hydroxychloroquine

- Unexpected ADR: Hypoglycemia
- Protective oral glucose tolerance test
- Reduced insulin requirements

Hydroxychloroquine

- Hypothesized Mechanism
- Reduced intracellular insulin degradation
- Increased intracellular insulin accumulation

Hydroxychloroquine

DM treatment:
- RA patients
  - Reduced incidence of DM
  - Effectiveness trial
  - “Significant reduction” in A1c over 6 months compared to placebo
  - About 1%

Hydroxychloroquine

- Clinical Significance
  - Potentially serious hypoglycemic events
  - Patient education
  - +/-Medication Adjustment

Patient Cases

- Patient Prescribed hydroxychloroquine
- Severe hypoglycemia
- Coma
- Hypoglycemia in NON-diabetic patient

Patient Scenario

JJ is a 49 year old female with a PMH significant for Type II DM on 70/30 (NPH/Regular) insulin 35 units BID started on hydroxychloroquine for RA.
What more would you like to know?

What do you want to do?
A. Counsel on Hydroxychloroquine’s potential for hypoglycemia
B. Empirically reduce insulin dose
C. Increase FSBG monitoring
D. Suggest taking hydroxychloroquine with a large serving of carbohydrates
E. Combination of above

Eccentric
“Deviating from the recognized or customary character, practice, etc”

The Eccentric

Diltiazem
• Class: Non Dihydropyridine Calcium Channel Blocker
• Indications: HTN, Angina, Antiarrhythmic
• MOA: Inhibits calcium from entering vascular and myocardial smooth muscle

Diltiazem
• Common Side Effects:
  • Constipation
  • Edema
  • Headache
  • Dizziness
Gingival Hyperplasia

- Time to manifestation
- Increased risk of other oral diseases
- Risk Factors
  - Age
  - Gingival Inflammation (gingivitis)
  - Dental plaque
    - Reservoir

Gingival Hyperplasia

- Cross sectional study of diltiazem and verapamil
  - Statistically significant difference
  - Diltiazem-increased risk of gingival enlargement

Gingival Hyperplasia

- Common Drug Induced Causes:
  - Cyclosporine: 27%
  - Phenytoin: 15-50%
  - Diltiazem:“Post marketing events reported infrequently”

Gingival Hyperplasia

- Diltiazem-rare but possible
  - Nifedipine more likely
  - Verapamil also possible
- Identify risk factors
- Proper oral hygiene

Pramipexole and Ropinirole

- Class: Dopamine Agonists
- Indications: Parkinson’s, Restless Leg Syndrome
- MOA: Direct dopamine agonist
Pramipexole and Ropinirole

• Common Side Effects
  • Orthostasis
  • Somnolence
  • Nausea/constipation
  • Dyskinesia
  • Fatigue

Hypothesized Mechanism

• Selectivity for D3 receptors
  • Pramipexole
  • Ropinirole

• Onset
  • 1-3 months
  • Up to 12-30 months

“Go For Broke”

Dopamine agonists implicated in compulsive gambling

Case Reports

• “54 year old married pastor…lost $2500 which he kept secret from his wife”
• “41 year old married computer programmer…losing $5000 within a few months”
• Purchased items he did not need or want
• “52 year old male lost $100,000
• Compulsively ate and gained 50 pounds
• Extramarital affairs and pornography

And several more…

Other Compulsive Behaviors

• Hypersexuality
• Compulsive Shopping
• Compulsive Eating
• Excessive engagement in hobbies

Common Theme

After discontinuation of dopamine agonists compulsions stopped

One month after stopping:
“All the problems are gone”
“I have my old husband back”
Patient Management

- Medication appropriateness
- Education
- Patient
- Friends/family
- Follow-Up

What Did We Learn?

Rewind

- No “Perfect Drug”
- Why care about ADR’s?
- ADR significance
- Examples
- Pathophysiology
- Patient management

Questions

- What Did We Learn?

References