Common Drug-Induced Diseases

Doing More Harm than Good

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Disclosure

I do not have (nor does any immediate family member have):
- a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity
- any affiliation with an organization whose philosophy could potentially bias my presentation

Objectives

- Define drug-induced disease (DID)
- Review the pathophysiology of several DIDs
  - Pulmonary fibrosis
  - Hyponatremia
  - QTc-interval prolongation
- Describe signs and symptoms of several DIDs
- Outline treatments of these DIDs
- Explain prevention strategies to reduce DIDs

DID Overview

- Drug-induced disease definition:
  - “An unintended effect of a drug that may result in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention and/or require hospitalization”
- Prevention is preferable to treatment
- Many drug-induced diseases are preventable
- High cost burden associated with DIDs

Costs of DIDs

- Cost-of-illness study from 2001 estimated drug-related morbidity and mortality annual costs of $177.4 billion
- Health care expenditure types:
  - Hospital admissions (70%)
  - Long-term care admissions (18%)
  - Physician visits (8%)
  - Emergency department visits (3%)
  - Additional prescriptions (1%)

Surveillance of DIDs

- Many DIDs are not identified prior to FDA approval
- Clinical trials not designed to identify all drug-related adverse events
- Smaller numbers of people exposed to drug in studies compared to patient population once approved
- Unforeseen side effects not discovered until large numbers of people taking the medication
- Post-marketing surveillance and adverse drug event reporting are important
- Report adverse drug events to FDA via MedWatch
Common Drug Classes Causing DIDs

- Antidiabetic medications: Hypoglycemia
- Antibiotics: Allergic reactions
- Non-steroidal anti-inflammatory drugs (NSAIDs): GI bleeding/anemia
- ACE inhibitors / Angiotensin Receptor Blockers (ARBs): Angioedema / acute renal disease
- Digoxin: Heart block / toxicity

Drug | Drug-Induced Disease
---|---
Antidiabetic medications | Hypoglycemia
Antibiotics | Allergic reactions
Non-steroidal anti-inflammatory drugs (NSAIDs) | GI bleeding/anemia
ACE inhibitors / Angiotensin Receptor Blockers (ARBs) | Angioedema/acute renal disease
Digoxin | Heart block/toxicity

Pulmonary Fibrosis

- Scarring of the lung parenchyma secondary to a chronic inflammatory process
- Accumulation of excess fibrous connective tissue leads to scars
- Causes thickening of bronchioles and alveoli
- Results in diminished oxygen exchange and reduced oxygen supply in blood

Symptoms of Pulmonary Fibrosis

- Chest pain (dull, primarily with inspiration)
- Cough (non-productive)
- Dyspnea
- Tachypnea
- Lung crackles
- Clubbing of the fingers
- Fatigue

Mechanisms of toxicity

- Oxygen free radicals are typically counterbalanced by antioxidants
- Drugs and chemicals produce lung toxicity through two basic mechanisms:
  1. Increased production of oxidants
  2. Inhibition of the antioxidant system

Risk Factors for Pulmonary Fibrosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Medications Associated with Each Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Nitrofurantoin (old)</td>
</tr>
<tr>
<td></td>
<td>Bleomycin (old), carmustine (young)</td>
</tr>
<tr>
<td>Age</td>
<td>Nitrofurantoin (young)</td>
</tr>
<tr>
<td></td>
<td>Bleomycin (old), carmustine (young)</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>Amiodarone, nitrofurantoin</td>
</tr>
<tr>
<td>cardiopulmonary surgery</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>---</td>
</tr>
<tr>
<td>Vinca alkaloid use</td>
<td>---</td>
</tr>
<tr>
<td>Pre-existing pulmonary disease</td>
<td>---</td>
</tr>
</tbody>
</table>

Incidence

- Carmustine: 20-30%
- Mitomycin: 10-35%
- Amiodarone: 10-15%
- Methotrexate: 3-7%
- Bleomycin: 4%
- Busulfan: 4%
- Nitrofurantoin: <1%
Pulmonary Fibrosis Treatment Options

- Discontinue offending medication
- Acute pneumonitis: Prednisone 40-80 mg/day
- Chronic fibrosis: Corticosteroid use is questionable
  - Consider prednisone if not improving with drug discontinuation
  - Amiodarone’s long half-life may delay recovery
- Taper corticosteroid therapy slowly over several weeks
- Perform pulmonary function testing to monitor for improvement


Hyponatremia

Hyponatremia Epidemiology

- Medications are a common cause of electrolyte abnormalities
- Hyponatremia is the most common electrolyte abnormality
  - Usually caused by syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Cost of treating hyponatremia in US $3.6 billion annually
- Associated with 7.6% increased hospital length of stay
- Increases 30-day hospital readmission rates


Medication Causes of Hyponatremia

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Most Likely for Hyponatremia</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Thiazide diuretics, hydrochlorothiazide, indapamide, chlorothalidone, others</td>
<td>Sodium excretion</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>SSRIs: sertraline, fluoxetine, paroxetine, citalopram, others: MAOIs, MAOIs, TCAs</td>
<td>SIADH</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Typical: Haloperidol, fluphenazine, thioridazine, Atypical: Aripiprazole, clozapine</td>
<td>SIADH</td>
</tr>
<tr>
<td>Antiepileptic agents</td>
<td>Carbamazepine, oxcarbazepine, valproic acid</td>
<td>SIADH</td>
</tr>
<tr>
<td>Chemotherapy agents</td>
<td>Vinca alkaloids, oxaliplatin, mitomycin, platinum compounds, doxorubicin, cisplatin</td>
<td>SIADH</td>
</tr>
<tr>
<td>Other</td>
<td>Other: cyclophosphamide, methotrexate</td>
<td>SIADH</td>
</tr>
</tbody>
</table>


Symptoms of Hyponatremia

<table>
<thead>
<tr>
<th>DECREASING</th>
<th>SYMPTOMS OF SEVERE/ACUTE HYponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Headache</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Lethargy</td>
</tr>
<tr>
<td>Seizures</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Coma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INCREASING</th>
<th>SYMPTOMS OF MILD/CHRONIC HYponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Nausea</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Gastric disturbances</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>Muscle cramps</td>
</tr>
</tbody>
</table>


SIADH Mechanism

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>Serum sodium level &lt; 135 mEq/L</td>
</tr>
<tr>
<td>Hyper-osmotic plasma urine</td>
<td>Plasma osmolality &lt; 280 mOsm/kg</td>
</tr>
<tr>
<td>Hyper-osmotic urine</td>
<td>Urine osmolality &gt; 100 mOsm/kg</td>
</tr>
<tr>
<td>Hypermoteric urine</td>
<td>Urine sodium level &gt; 30 mEq/L</td>
</tr>
</tbody>
</table>

John Wiley & Sons, Inc. 2007.
Medication Alternatives in Hyponatremia

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Lower Potential for Hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Loop diuretics: furosemide, bumetanide, torsemide</td>
</tr>
<tr>
<td></td>
<td>Potassium-sparing diuretic: Spironolactone</td>
</tr>
<tr>
<td></td>
<td>Alternative blood pressure agent classes</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Mirtazapine, bupropion, milnacipran</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Olanzapine, risperidone</td>
</tr>
<tr>
<td>Antiepileptic agents</td>
<td>Levetiracetam, lamotrigine, gabapentin</td>
</tr>
<tr>
<td>Chemotherapy agents</td>
<td>Cyclophosphamide hydrate with isotonic saline solution instead of water; use alternative agents when possible</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Use alternative agents when possible: Amiodarone → dronedarone or other antiarrhythmic</td>
</tr>
<tr>
<td></td>
<td>Proton pump inhibitors → β-blockers</td>
</tr>
<tr>
<td></td>
<td>Opiates or NSAIDs → acetaminophen, topical lidocaine</td>
</tr>
</tbody>
</table>


Risk Factors for Hyponatremia

- Advancing age (≥65 years)
- Concomitant diuretic administration
- Female sex
- Lower body mass index
- Baseline serum sodium < 139 mEq/L
- Higher doses of medications
- Elevated serum drug concentrations (antiepileptics)
- Asian race (vinca alkaloids)

Tisdale J. Drug-Induced Diseases. ASHP 2005.

Prevention of Hyponatremia

- Use the lowest-possible therapeutic doses
- Use agents with lower SIADH-causing potential
- Avoid coadministration with thiazide diuretics
- Avoid polypharmacy and drug-drug interactions
- Monitor serum sodium concentrations 1-2 weeks after initiation of treatment, especially in those with risk factors
- Monitor for symptoms: fatigue, anorexia, confusion, falls
- Advise against excessive fluid intake

Tisdale J. Drug-Induced Diseases. ASHP 2005.

Hyponatremia Treatment Options

- Discontinue the offending agent
- Switch to an alternative agent
- Fluid restriction (≤ 1 liter/day)
- Isotonic saline + loop diuretic: furosemide 20-40 mg/day
- Demeclocycline 150-400mg orally 3 times a day
- Urea powder 15-60g orally daily
- Tolvaptan 15-30 mg orally daily
- Hypertonic saline (acute or symptomatic patients only)


Hyponatremia Treatment Pathway

Acute (<48 hours) or Symptomatic
- Severe Symptoms: 3% saline bolus: 100 mL over 10 mins up to 3 doses
- Moderate Symptoms: 3% saline continuous infusion (0.5-2 mL/kg/hr)

Chronic (>48 hours) or Asymptomatic
- First line: fluid restriction (≤ 1 liter/day)
- Second line: US Guidelines: demeclocycline, urea, or tolvaptan
- European Guidelines: urea, loop diuretic + oral NaCl

Serum Sodium Correction Rates
- Normal Risk of ODS: <10-12 mEq/L/24h
- High Risk of ODS: <8 mEq/L/24h

ODS: osmotic demyelination syndrome

QT Prolongation / Torsades de Pointes

- Ventricular arrhythmia that can lead to sudden cardiac death
- Most common cause of drug withdrawal from the market or restriction of medication use
- Dozens of medications can contribute to QT prolongation
- Onset of noncardiac drug-induced torsades de pointes:
  - <72 hours: 18%
  - Between 3 – 30 days: 42%
  - > 30 days: 40%

Tisdale J. Drug-Induced Diseases. ASHP 2005.

Symptoms of Torsades de Pointes

- Heart palpitations
- Syncope
- Dizziness
- Shortness of breath
- Chest pain
- Cold sweats
- Nausea

Tisdale J. Drug-Induced Diseases. ASHP 2005.

Risk Factors for Torsades de Pointes

- QTc interval >500 ms
- Increase in QTc interval by >60 ms from baseline
- Female sex
- Hypokalemia and/or hypomagnesemia
- Advancing age (≥65 years)
- Bradycardia
- Left ventricular dysfunction
- Administration of multiple QT-prolonging medications
- Increased doses of medications (especially in renal dysfunction)
- Rapid IV infusion of torsades-inducing drugs

Tisdale J. Drug-Induced Diseases. ASHP 2005.

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Risk Potential for QT Prolongation</th>
<th>Lower Potential for QT Prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical antipsychotics</td>
<td>Thioridazine, haloperidol, droperidol, chlorpromazine, pimozide</td>
<td>Loxapine</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>Ziprasidone,isperidone,quetiapine</td>
<td>Olanzapine,risperidone,quetiapine</td>
</tr>
<tr>
<td>SSRI</td>
<td>Citalopram, escitalopram</td>
<td>Paroxetine,fluoxetine,sertraline,fluvoxamine</td>
</tr>
<tr>
<td>TCA and TCAs</td>
<td>Amitriptyline,imipramine,maprotiline,nortriptyline,desipramine,clomipramine</td>
<td>Doxepin</td>
</tr>
<tr>
<td>SNRI</td>
<td>Venlafaxine</td>
<td>Duloxetine,desvenlafaxine,levetrazapram,mirtazapine</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>Mirtazapine</td>
<td>Bupropion,vorvafline,vinlzen,datalone</td>
</tr>
<tr>
<td>Dieter A. US Pharmacist 2015</td>
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Tisdale J. Drug-Induced Diseases. ASHP 2005.
Prevention of Torsades de Pointes

- Avoid QT-prolonging drugs when baseline QTc > 450 ms
- Discontinue QT-prolonging drugs when QTc > 500 ms
- Maintain serum potassium > 4 mEq/L
- Maintain serum magnesium > 2 mEq/L
- Avoid QT-prolonging agents when LVEF < 20%
- Renally adjust medication doses
- Avoid use of concomitant QT-prolonging drugs
- Infuse IV QT-prolonging drugs slowly

Tisdale J. Drug-Induced Diseases. ASHP 2005.

Initial Torsades de Pointes Management

**Hemodynamically Unstable**
- Synchronized cardioversion

**Hemodynamically Stable**
- Magnesium 1-2g IV over 5-10 minutes (may repeat up to 12g)
- Temporary pacemaker
- Isoproterenol 2-10 mcg/min IV titrated to heart rate
- IV lidocaine bolus/infusion
- IV phenytoin 10-15 mg/kg

Tisdale J. Drug-Induced Diseases. ASHP 2005.

Conclusions

- DIDs are extremely costly but preventable
- Pharmacists are on the front lines of identifying DIDs
- Ensure medications are dosed appropriately for age, renal function, etc.
- Be alert for drug side effects and interactions
- Counsel patients about symptoms that warrant medical attention
- Recommend alternative medications when toxicity or side effects are a concern

Tisdale J. Drug-Induced Diseases. ASHP 2005.