How drugs affect our ability to diagnose and treat our patients

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Clinical Practice

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  - Inpatient Acute Care Oncology
Conflicts of Interest

- I have no conflicts of interest to declare
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General Outline

• Drugs that may affect diagnosis
  • What is a radiopharmaceutical?
  • What are radiopaque contrast media?
    • What can interact with contrast dyes?
• Drugs that may affect radiation treatment (RT)
  • Antioxidants
• Basic pharmacology of drugs that are often used
  • Benzodiazepines
  • Antiemetic agents
  • Pain medications
Learning Objectives

• Identify agents that may affect diagnostic imaging
• Recognize medications that may increase the adverse effects of diagnostic imaging agents
• Evaluate the interaction between antioxidants and radiation therapy
• Review the pharmacology of commonly used medications
• Recognize the role of the pharmacist in radiopharmaceuticals
What is a Radiopharmaceutical?

- Tracers for medical imaging
- Used for diagnosis, therapeutic, or investigations
- Designed to be selective and specific for a particular organ or tissue
- Short half lives
What is a Radiopharmaceutical?

• Short half life provides challenges
• Many different radiopharmaceuticals and radionuclides used for many different imaging
• Decay leaves radiotracer to allow for imaging
  • Gallium-67
  • Indium-111
  • Strontium-82
  • Technetium-99
  • Thallium-201

https://www.isotopes.gov/outreach/med_isotopes.html
Technetium-99

• Most widely used
• Half life: 6 hours
  • Radioactivity of isotope to reach half the original value
  • Drugs: Time to reach half of its original concentration
• Different applications
  • Brain
  • Heart
  • Liver
  • Lungs
  • Thyroid
  • Kidney

https://www.isotopes.gov/outreach/med_isotopes.html
DIAGNOSTIC IMAGING
RADIOPAQUE CONTRAST MEDIA
Case 1

• 65 year old man with abdominal pain requiring investigation
• CT scan of abdomen scheduled
• Allergies: Shellfish
• Medical History:
  • Hypertension
  • Diabetes
  • Osteoarthritis
• Medications:
  • Ramipril 5 mg once daily
  • Metformin 500 mg twice daily
  • Acetaminophen 1000 mg as needed for pain
What are Radiopaque Contrast Media?

- Used in radiography and fluoroscopy
- Distinguish borders between tissues
- Most agents are iodine based
  - Ionic – salts hyperosmolar. Can be neurotoxic
  - Nonionic – Low osmolality. Fewer adverse effects
- Newer agents are less osmolar and not iodine based
- Allergic reactions
- Contrast nephropathy

Contrast Dye Allergy

- Reactions may vary
  - Mild – cough, itching
    - Diphenhydramine
  - Moderate – dyspnea, changes in blood pressure
    - Diphenhydramine
  - Severe – respiratory distress, arrhythmias, anaphylaxis
    - Epinephrine
- Risk factors for anaphylaxis:
  - Previous reaction to contrast dyes
  - Asthma
  - Other allergies
- Premedication
Contrast Dye Nephropathy

- Kidney damage induced by contrast dyes
- Increase in serum creatinine
  - Marker for kidney damage
  - Usually within 24 hours
- Risk factors:
  - Pre-existing kidney damage
  - Diabetes
  - Hypertension
  - Heart failure
  - Multiple myeloma
  - Age > 70
  - Dehydration
  - Medications

Metformin

- Antidiabetic medication
- Half life: 4 – 9 hours
- Excretion: 90% in the urine unchanged by active secretion
- Renal impairment can lead to lactic acidosis
- Risk factors for lactic acidosis:
  - Acute congestive heart failure
  - Dehydration
  - Excessive alcohol intake
  - Prior renal impairment
Metformin

• RECOMMENDATION:
  • Hold before CT scan and for 48 hours after scan
  • Confirm that renal function is normal

*For normal renal function with no comorbidities, American College of Radiology guidelines state discontinuation of metformin may not be necessary

Contrast Dye Nephropathy

- IF NEPHROPATHY OCCURS:
  - Stop metformin immediately and do not restart
  - Other renal toxic medications may compound the effect
  - Medications eliminated by the kidneys may require adjustment or stopping

Your pharmacist can help!
Metformin

• Holding metformin may increase blood sugars for a few days
  • Watch diet? Monitor blood glucose level?
• Hyperglycemia complications require a long time to develop
  • Macrovascular (cardiac)
  • Microvascular (eyes, kidneys, feet)
• Extremely high sugars can be dangerous
  • Diabetic ketoacidosis or hyperglycemic hyperosmolar state
  • These are rare circumstances
Shellfish Allergy

- Theory: Allergy to shellfish predisposes an individual to have a reaction to contrast dyes
  - Iodine allergy?
Shellfish Allergy

• Shellfish allergies are to the proteins and not the essential trace nutrient of iodine

• Literature review
  • Reactions varied from 0.2 – 17%
  • History of previous reaction to dyes result in 7 – 17% mild reactions but no increase in severe reactions
  • Severe reactions 0.02 – 0.5%
  • No difference between shellfish allergy and other food allergies or asthma
Shellfish Allergy Summary

• Individuals with allergies are at increased risk of anaphylactic reactions
  • Not limited to shellfish allergies
• Severe and anaphylactic reactions are rare but possible
RADIATION THERAPY
ANTIOXIDANTS
Case 2

• 60 year old woman with head and neck cancer being treated with RT
  • Allergies: No known
  • Medications: No prescriptions
  • Vitamins/Herbal products:
    • Greens (super antioxidant)
    • Vitamin C 1000 mg daily
    • Melatonin 40 mg daily
    • Multivitamin
  • Smoking history: Pack per day for 30 years. Quit for 1 year
Herbal Product Use

• Increasing use of natural products and complementary alternative medicines (CAMs)
• Varying percentages in literature
  • 6 – 84%
  • Higher in cancer patients?
• Lack of evidence
• Lack of safety
• Lack of regulation
Radiation Therapy

- Mechanism of cell death still being investigated
- Prevalent theory
  - Double stranded breaks in DNA leading to cell death
  - Ionization
  - *Indirect ionization through generation of free radicals*
  - Affect cell cycle
Free Radicals

Formation of Free Radicals

- UV Light
- Ionizing Radiation
- Smoking
- Metabolism
- Inflammation
- Air Pollution

Mitochondrion

DNA Damage

White blood cell

http://www.activ-balance.com/images/health2b_pic3.jpg
Antioxidants

- Endogenous antioxidant effects
  - Glutathione
  - Superoxide dismutase
  - Catalase
- Vitamins
  - Ubiquinone (Vitamin Q, Coenzyme Q10)
  - Retinol (Vitamin A)
  - Tocopherol (Vitamin E)
  - Ascorbic (Vitamin C)
  - Carotenoids
Antioxidants

- Phytochemicals
  - Melatonin
  - α-lipoic acid
  - Polyphenols
  - Coumarin
  - Curcumin
- Amino acids
  - N-acetylcysteine
  - L-arginine
- Minerals
  - Zinc
  - Selenium
Antioxidant Review

• Review of evidence
  • Majority have no significant difference
  • Few studies with survival rates in supplementation groups slightly lower
  • High dose vitamin C and melatonin seem to have protective effects for cancer cells during RT
  • Smokers and α-lipoic acid or β-carotene significantly increases mortality and recurrence
  • Minimal to no effect on reduction of adverse effects from RT
  • No reduction in cancer but may accelerate tumor growth?
Take Home Message

- Evidence is limited for improvement of symptoms or prevention of cancer
- May affect the outcomes of our treatment
- Some populations may have negative effects
- Interaction? Safety? Patient perspective?
- Which herbals are actually antioxidants?

Your pharmacist can help!
PHARMACOLOGY
Benzodiazepines

• Sedative-hypnotic class of medications
  • Sedative = relieve anxiety (anxiolytic), cause sedation
  • Hypnotic = induce sleep
  • Anaesthesia at high doses
• Other clinical uses
  • Anticonvulsant
  • Muscle relaxation
GABA = major inhibitory neurotransmitter in CNS

Benzodiazepines enhance effects of GABA – more openings of channel
## Benzodiazepines: “PAM”s

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Minutes (given IV)</td>
<td>1-4 hrs</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>1-3 hrs</td>
<td>12-15 hrs</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1-3 hrs</td>
<td>20-60 hrs</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1-3 hrs</td>
<td>10-20 hrs</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>&gt; 3 hrs</td>
<td>5-25 hrs</td>
</tr>
<tr>
<td>Temazepam</td>
<td>1-3 hrs</td>
<td>10-20 hrs</td>
</tr>
<tr>
<td>Diazepam</td>
<td>&lt; 1hr</td>
<td>100 hrs</td>
</tr>
</tbody>
</table>

Adapted from e-CPS monograph: Benzodiazepines
Benzodiazepines

• Can be associated with
  • Tolerance - decreased responsiveness to a drug following repeated exposure
  • Dependence - an altered physiologic state that requires continuous drug administration to prevent an abstinence or withdrawal syndrome
  • Addiction - drug use may become compulsive (abuse potential)

• Targeted/Controlled substance
  • Specific rules for dispensing, storing, prescribing in Canada
  • https://pharmacists.ab.ca/benzodiazepines-other-targeted-substances
Adverse Effects

- CNS depression
  - Drowsiness
  - Dizziness
  - Decreased awareness
- Loss of memory
- Paradoxical agitation
- Withdrawal effects
  - Abrupt discontinuation after long term use
Antiemetics

- Can prevent and/or treat chemotherapy and radiation induced nausea and vomiting
  - 5-HT3 antagonists
  - Corticosteroids
  - Dopamine receptor antagonist
  - NK1 antagonist (CINV)
The diagram illustrates the process of vomiting in response to chemical stimuli (CHEMO). It shows the connections between the gastrointestinal tract, the Chemoreceptor Trigger Zone (CTZ), and the Vomiting Center (VC). Key points include:

- **CHEMO**
  - Enterochromaffin cells of GI tract
  - Serotonin release
  - 5-HT3 receptors

- **CTZ**
  - Stimulates VC
  - Controls

- **VC**
  - Controls
  - 5-HT3 receptors
  - NK1 receptors
  - Dopamine receptors

- **Chemoreceptor Trigger Zone**
  - 5-HT3 receptors
  - NK1 receptors
  - Dopamine receptors

Additional reactions triggered by CHEMO include:

- Salivation
- Respiratory rate
- Pharyngeal, GI, and abdominal muscle contractions

The diagram also highlights the involvement of the vagus nerve and afferent fibers in the control and response mechanisms.
5-HT3 Antagonists

- Have potent antiemetic properties that are mediated in part through central 5-HT₃-receptor blockade in the vomiting center and chemoreceptor trigger zone but mainly through blockade of peripheral 5-HT₃ receptors on extrinsic intestinal vagal and spinal afferent nerves
- Adverse effects: headache, dizziness, constipation

- Ondansetron 8 mg
- Granisetron 2 mg
- Palonosetron (greater affinity for receptor but not yet routinely used here)
Dexamethasone

- Glucocorticoid corticosteroid
- 60-80% absorbed orally
- $T_{\text{max}}$: 1-2 h (PO, IM); 5-10 min (IV)
- Plasma $t_{\frac{1}{2}}$: ~4 h; biological $t_{\frac{1}{2}}$: 36-54 h
- Hepatically metabolized
- 10% renal excretion
- MOA for nausea prevention not established
## Dexamethasone Basics

### Relative Potencies and Equivalent Doses of Common Corticosteroids

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Relative Antiinflammatory Activity</th>
<th>Relative Mineralocorticoid Activity</th>
<th>Equivalent Dose (mg)</th>
<th>Plasma Half-life (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>0.8</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1.0</td>
<td>1.0</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4.0</td>
<td>0.8</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4.0</td>
<td>0.8</td>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5.0</td>
<td>0.0</td>
<td>4.0</td>
<td>300</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5.0</td>
<td>0.0</td>
<td>4</td>
<td>180</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25.0</td>
<td>0.0</td>
<td>0.75</td>
<td>100–300</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25–30</td>
<td>0.0</td>
<td>0.75</td>
<td>100–300</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>10</td>
<td>125</td>
<td>—</td>
<td>200</td>
</tr>
</tbody>
</table>

Source: Pharmacotherapy © 2007 Pharmacotherapy Publications
Common Side Effects

- Stomach irritation
- Increased energy/appetite
- Insomnia
- Increased blood sugars
- Increased blood pressure
- Long term effects
  - Cushing’s Syndrome
  - HPA-Adrenal Axis Suppression
  - Muscle weakness
  - Osteoporosis
  - Infection risk
Dopamine Receptor Antagonists

• Prochlorperazine 10 mg
  • Belongs to a class of antipsychotic medications called phenothiazines
  • Antiemetic properties are mediated through inhibition of dopamine and muscarinic receptors

• Metoclopramide 10 mg
  • Blocks dopamine receptors
  • Enhances the response to acetylcholine of tissue in upper GI tract causing enhanced motility and accelerated gastric emptying

• These agents typically used as needed, commonly added to antiemetic regimens as rescue medications
Opioids

- Opium – source of morphine derived from the poppy seed
- Stronger analgesics that work on the opioid receptors in the CNS
  - Mu receptor
  - Delta receptor
  - Kappa receptor
- Often used in severe pain

- Morphine, codeine, hydromorphone, oxycodone, fentanyl, methadone
### TABLE 31-2 Common opioid analgesics.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Receptor Effects</th>
<th>Approximately Equivalent Dose (mg)</th>
<th>Oral:Parenteral Potency Ratio</th>
<th>Duration of Analgesia (hours)</th>
<th>Maximum Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>+++</td>
<td>+</td>
<td>10</td>
<td>Low</td>
<td>4–5</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>+++</td>
<td></td>
<td>1.5</td>
<td>Low</td>
<td>4–5</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>+++</td>
<td></td>
<td>1.5</td>
<td>Low</td>
<td>3–4</td>
</tr>
<tr>
<td>Methadone</td>
<td>+++</td>
<td></td>
<td>10</td>
<td>High</td>
<td>4–6</td>
</tr>
<tr>
<td>Meperidine</td>
<td>+++</td>
<td></td>
<td>60–100</td>
<td>Medium</td>
<td>2–4</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>+++</td>
<td></td>
<td>0.1</td>
<td>Low</td>
<td>1–1.5</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>+++</td>
<td>+</td>
<td>0.02</td>
<td>Parenteral only</td>
<td>1–1.5</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>+++</td>
<td></td>
<td>Titrated</td>
<td>Parenteral only</td>
<td>0.25–0.75</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>+++</td>
<td></td>
<td>Titrated³</td>
<td>Parenteral only</td>
<td>0.05⁴</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>+++</td>
<td></td>
<td>2–3</td>
<td>High</td>
<td>4–5</td>
</tr>
<tr>
<td>Codeine</td>
<td>±</td>
<td></td>
<td>30–60</td>
<td>High</td>
<td>3–4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>±</td>
<td></td>
<td>5–10</td>
<td>Medium</td>
<td>4–6</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>++</td>
<td></td>
<td>4.5</td>
<td>Medium</td>
<td>3–4</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>±</td>
<td>+</td>
<td>30–50</td>
<td>Medium</td>
<td>3–4</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>—</td>
<td>++</td>
<td>10</td>
<td>Parenteral only</td>
<td>3–6</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>±</td>
<td>—</td>
<td>0.3</td>
<td>Low</td>
<td>4–8</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>±</td>
<td>+++</td>
<td>2</td>
<td>Parenteral only</td>
<td>3–4</td>
</tr>
</tbody>
</table>
Adverse Effects

- CNS depression
  - Drowsiness
  - Dizziness
  - Decreased awareness
- Constipation
- Nausea/vomiting
- Tolerance/dependence
- Hypotension
- Respiratory depression
Narcotics

- Tightly controlled and regulated by government
- Specific rules for dispensing, storing, prescribing in Canada
- Triplicate program
  - Specific medications and provincial program
  - Different prescription pad and requires physician registration with program
    - [http://www.cpsa.ab.ca/Services/Triplicate_Prescription_Program/Generic_Medication_List.aspx](http://www.cpsa.ab.ca/Services/Triplicate_Prescription_Program/Generic_Medication_List.aspx)
- Methadone prescribers require methadone exception granted by Health Canada
Acetaminophen

• Treatment of mild to moderate pain
  • Dose can vary from 325 mg – 1000 mg per dose
  • Regular strength is 325 mg and extra strength is 500 mg
• Antipyretic
• No anti-inflammatory effect
• Peak concentrations in 30-60 minutes, half life 2-3 hours
• Safe at doses less than 4000 mg daily
• Hepatotoxicity can occur with high doses/chronic use
Role of the Pharmacist
Role of the Pharmacist

• Pharmacists not often involved or trained in dispensing radiopharmaceuticals and contrast dyes
• Finding drug interactions
• Evaluation of drug therapy
• Manage with complications and supportive care
  • Allergic reactions
  • Nephropathy
Thank you!

Questions?