AN OUTPATIENT PHARMACY APPROACH TO PEDIATRIC ONCOLOGY

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Disclosures

- No relationships to disclose

Pharmacist Objectives

- Discuss considerations relating to pediatric medication dosing and administration
- Identify the most common types of pediatric cancer
- Identify treatment regimens for chemotherapy-induced nausea and vomiting
- Develop an overall understanding of oral chemotherapy agents
- Discuss the safety of over-the-counter medications in a pediatric oncology patient
- Be able to recognize when to recommend a pediatric oncology patient to the emergency department

Technician Objectives

- Discuss considerations relating to pediatric medication dosing and administration
- Be able to recognize appropriate oral chemotherapy dosing
- Develop an understanding of handling and dispensing oral chemotherapy agents
- Identify appropriate over-the-counter medications for pediatric oncology patients
- Be able to recognize a pediatric oncology patient who needs emergency care

Pediatric Dosing and Administration

Pediatric Dosing Considerations

- Age
- Weight
- BSA
- Indication
- Max dose
- Renal or hepatic adjustments
- Interactions
- Continuously changing

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Routes of Administration

- Oral
- G-tube, etc.
- IV
- IM
- SQ
- IO
- Emergency only

Absorption\(^1\,^2\,^3\)

- Gastric pH neutral then falls to pH 2-3 around 3 year
- Gastric emptying time slower during first week of life
- Gastric-enteral transit time reduced in adults about 3 years of age
- Diet
- Pediatric formulations
- IM absorption
- Volume of administration based on age and weight
- Topical absorption

Absorption of hydroxy-tetrahydrocannabinol - potency - edibles - first - pass - metabolism

Distribution\(^1\,^2\,^3\)

- Based on body composition
- Water vs. fat
- Composition of medication
- Protein binding
- Amount of protein
- Decreased affinity for medications
- Drug transporters

Pediatric Volume of Distribution\(^1\,^2\,^3\)

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Body Water (%)</th>
<th>Extracellular Fluid (%)</th>
<th>Adipose Tissue (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature Neonate</td>
<td>92</td>
<td>50</td>
<td>1 – 5</td>
</tr>
<tr>
<td>Term Neonate</td>
<td>75</td>
<td>35</td>
<td>12 – 16</td>
</tr>
<tr>
<td>3 mo.</td>
<td>73</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>1 yr.</td>
<td>59</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Adult</td>
<td>60</td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>

Metabolism: CYP Enzymes\(^1\,^2\,^3\)

<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>CYP2D6</th>
<th>CYP2C19</th>
<th>CYP3A4</th>
<th>CYP3A7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
<td>Minimal total activity; increased adults in infancy then tapered down</td>
<td>Polymorphic Rapid vs Slow Metabolism</td>
<td>Activity increase in first 2 weeks</td>
<td>Low at birth, Rapid 1 month increases in gut mucosa</td>
</tr>
<tr>
<td>Targets</td>
<td>Caffeine, Theophylline</td>
<td>Codeine and many others (psych)</td>
<td>AEDs and PPIs</td>
<td>~40% of all drugs</td>
</tr>
</tbody>
</table>
Phase II Metabolism\(^1,2,3\)
- Inactivates compounds → increases water solubility and excretion
- Phase II enzymes found in mostly in liver but also in kidneys and lungs
- Glucuronidation accomplished by UGT
  - Mostly decreased in infants
  - Potential toxicity of APAP, morphine, zidovudine

Elimination\(^1,2,3\)
- Renal blood flow is lower at birth
- Increases during first year of life
- Bedside Schwartz (1-18yr)
  - GFR (mL/min/1.73 m\(^2\)) = 0.413 x length/SCr

Pharmacodynamics\(^1,2,3\)
- How the drug affects the body
- Greater affinity for medications
- May have fewer receptors
- Paradoxical drug effects
- Growth and development
- Adverse drug reactions
  - Aspirin, propylene glycol, cough products

Pediatric Cancers

Acute Lymphoblastic Lymphoma (ALL)\(^4\)
- Most common malignancy in children between birth and 14 years
- Abnormal proliferation of precursor B cell or T cell lymphocytes
- Diagnosis based on evaluation of blood and bone marrow
- Genetic component
  - Nonspecific signs/symptoms
  - Fever, bleeding, bone pain, lymphadenopathy, hepatosplenomegaly
  - Corticosteroids important part of therapy among many other chemotherapy agents
- Depending on factors 5 year Overall Survival (OS) > 90%

Acute Myeloid Leukemia (AML)\(^5\)
- Less common than ALL
- Proliferation of abnormal myeloid, erythroid, monocytic, megakaryocytic cell precursors
- Fever, malaise, bone pain, cytopenia, coagulopathies
- Diagnosis on pathology of blood and bone marrow
- Event free survival and overall survival
  - 50% and 60-70%, respectively
Neuroblastoma
- Most common extracranial solid tumor of childhood
- Peaks <4 years and median age of 19 months
- Begins in nerve tissue of adrenal glands (most common), neck, chest, abdomen, pelvis
- Genetic component
- Signs and symptoms
  - Fever, SOB, petechiae, high blood pressure, uncontrolled muscle and eye movements, droopy eyelids
  - Increase in catecholamine release

Oral Chemotherapeutic Agents

Chemotherapy Dosing
- Dose by BSA (m²) or weight (kg)
  - Less than 1 year old is weight
  - Greater than 1 year can be weight or BSA
- Should wear appropriate gear when manipulating medication
- Handle with caution if pregnant
- Standard doses may not be available
- Liquids are better in many cases due to dose variation

NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings
- Reduction in occupational hazards and safe-handling precautions
- Medications that pose reproductive and developmental toxicity
  - Take caution with medication preparation
    - Crushing
    - Splitting tablets
  - Use already prepared liquid, if available
  - Appropriate PPE and manipulated in appropriate engineering controls
  - Check literature if a medication is not on this list
Methotrexate7,10
- Essential treatment for leukemia, lymphoma, osteosarcomas
- Maintenance in ALL protocols
- Adverse effects
  - Acute Kidney Injury
  - Nausea/Vomiting
  - Myelosuppression
  - Mucositis
  - Avoid drugs that will increase levels
  - Requires hydration and rescue therapy
  - Mainly IV and large doses
  - Liquid and tablet formulations

Tyrosine Kinase Inhibitors8,10
- Imatinib and Dasatinib
- BCR-ABL inhibitor
- Ph+ ALL, CML
- Adverse effects
  - Myelosuppression
  - Elevated LFTs
  - Nausea, rash, edema, muscle cramps
  - Drug interactions
  - Avoid PPI or H2 blockers (dasatinib)
  - Tablets
  - Extemporaneous preparation (imatinib)
  - Dissolve in apple juice

6-Mercaptopurine9,10
- Purine analog that incorporates itself into DNA and inhibits synthesis
  - ALL
- Adverse effects
  - Myelosuppression
  - Mucositis
  - Rash, photosensitivity
  - Hepatotoxicity
- Drug interactions
  - Dose adjust for TMPT deficiency
  - Homozygous deficiency
- Tablet, suspension, or extemporaneous preparation
  - Take on empty stomach
  - Ok to crush

Isotretinoin10
- Decreases cell proliferation and induces differentiation
- Recurrent neuroblastoma
- Adverse effects
  - Skin reactions
  - Growth effects
  - Neutropenia
  - LFT elevation
  - Pancreatitis
  - Photosensitivy
  - REMS Program – teratogenic defects
  - Capsules
  - Extemporaneous preparation
  - Swallow whole with a meal

Corticosteroids10
- Dexamethasone and prednisone
- Inhibition of inflammatory mediators and suppression of immune system
- Used in ALL
  - Dexamethasone has better CNS penetration and is more potent
  - Dexamethasone in < 10 yrs and prednisone in > 10 yrs
- Adverse effects
  - Cardiovascular
  - CNS
  - Endocrine
  - Osteoporosis
  - Adrenal suppression
  - Infection

Corticosteroids10
- Tablets, liquid, injections
- Taper down
- Be aware with concomitant administration of live vaccinations and high doses
- Dexamethasone is longer acting
- Can be a problem if given to a new diagnosis of ALL prior to diagnosis
Etoposide
- Topoisomerase II inhibitor
- Cause DNA strand breaks
- Oral used for comfort care
- Adverse effects
  - Myelosuppression
  - Nausea and vomiting
- Oral capsules and extemporaneous preparation
- Counsel on comfort care measures

Chemotherapy Induced Nausea Vomiting (CINV)

CINV Guidelines
- Pediatric Oncology Group of Ontario (POGO): Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients
- Children’s Oncology Group (COG): Guidelines on Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients

Emesis Definition
- Acute emesis
  - Occurs within first 24 hours after chemotherapy
  - In absence of effective prophylaxis it can occur within a few hours of chemotherapy initiation
- Delayed emesis
  - Greater than 24 hours after chemotherapy delivery
  - Cisplatin, cyclophosphamide are offenders
- Anticipatory emesis
  - Conditioned response to previous administration of chemotherapy
  - Association between chemotherapy and nausea
Non-pharmacological

- Eat small, more frequent meals
- Odor control
- Avoid spicy, fatty, high salty foods
- Use measures that have helped in past

Highly Emetogenic Chemotherapy

- Aprepitant used in patients > 6 months old!
- NK1-receptor antagonist
- Monitor drug interactions
- 5-HT3 antagonist + dexamethasone
- Ondansetron, granisetron, palonosetron
- Do not use dexamethasone for CINV in ALL
- Anti-emetic drip (inpatient)
  - Dexamethasone, diphenhydramine, metoclopramide, lorazepam if anticipatory

Moderate-Low Emetogenic Chemotherapy

- Moderate
  - 5-HT3 receptor antagonist + dexamethasone
  - Ondansetron, granisetron, palonosetron
  - If > 6 months and cannot receive dexamethasone then ok to use aprepitant
- Low
  - 5-HT3 antagonist
  - Ondansetron, granisetron, palonosetron

Anticipatory CINV

- Hypnosis, acupuncture?
- Use same agents as listed above
- Lorazepam

Breakthrough CINV

- Metoclopramide (> 1 y/o)
- Extrapyramidal reactions
- Olanzapine
- Diphenhydramine
- Promethazine
- Lorazepam
- Scopolamine patches
- Dronabinol
Olanzapine

- Second generation antipsychotic
  - Antagonism of serotonin, dopamine, histamine, and alpha-1-adrenergic receptors
- Drug interactions
  - Antipsychotic
  - Antimalarial
  - Antihistaminic
  - Anticholinergic
  - Antiepileptic
  - Antiparkinsonian
  - Antihypertensive
  - Anticoagulant
- Adverse effects
  - Hypotension
  - Hyperglycemia
  - Hypertension
  - Hypothermia
  - Tachycardia
  - Tachypnea
- Drug interactions
- Adverse effects

Olanzapine for Prevention of CINV

- Randomized, double-blind, phase 3 trial
  - Patient 18+ with malignant disease who had not received chemotherapy
  - 5-HT3-receptor antagonist, dexamethasone, NK1-receptor antagonist + olanzapine (10mg x 4 days) or placebo
  - Stratified by sex, chemotherapy regimen (cisplatinum vs. anthracycline + cyclophosphamide containing), and 5-HT3-receptor antagonist
  - Primary outcome – no nausea during assessment period of 120 hours

Olanzapine in Adults

- Meta-analysis (Cochrane Review)
  - Highly and moderate emetogenic
  - Olanzapine vs. placebo
  - Likelihood of being free from nausea or vomiting during chemotherapy (RR 1.98, 95% CI 1.59 to 2.47; participants = 561; studies = 3; I² = 0%)
  - About 5 days of treatment
  - Probably reduces delayed nausea with acute nausea and vomiting being uncertain

Olanzapine in Pediatrics: Multi-center, prospective, open-label, feasibility

- Flank, J., Schechter, T., et al.
  - English speaking; 4-18 y/o; ≥ 14kg
  - Olanzapine 0.14 mg/kg/dose (max 10 mg/dose; 2.5 mg increments) x 4 doses (max) + standard of care
  - Dose decreased if patient experienced undesirable sedation
  - Feasibility of recruitment, compliance, and adverse effects for endpoints
  - Endpoints were met
  - Free of vomiting and retching on 85 ± 91% of acute phase days
  - All but 1 patient experienced nausea
  - Free of vomiting and retching on 75 ± 53% and free of nausea on 50 ± 33% of delayed phase days
  - Mild sedation was main adverse effect

Olanzapine in Pediatrics: Retrospective, Multi-Center Review

- Flank, J., Thackray, J., et al.
  - Patients < 18 y/o who received olanzapine for CINV in acute phase of chemotherapy block
  - Primary outcome - # times vomited in acute phase
Olanzapine in Pediatrics: Retrospective, Multi-Center Review

OTC Safety Considerations
- Drug-drug interactions!!
- Drug-disease interaction
- NSAIDs
- Herbs
  - Some families believe that herbs will work better than western medicine
  - Limited data
  - Including homeopathic
  - CBD oils
- Mucositis
  - Inflammation and ulceration of oral mucosa
  - Secondary to immunosuppression, chemotherapy, and radiatrion
  - Decreased quality of life
  - Increase risk of bacterial and fungal infection
  - Decrease nutritional status
  - Pain management
    - Narcotics
    - Magic mouthwash
    - Oral hygiene

Honey for Mucositis

Probiotics in Pediatric Oncology
- Insufficient data
- Which strains of probiotics are most beneficial?
- Outcome of probiotics?
  - Decrease in diarrhea
  - Improved overall health
  - Preserve gut function
  - Infectious in immunocompromised patients?
    - Lot’s of research and data both supporting and refuting probiotics
  - Dosing?
Safety and Feasibility of Probiotics in Hematopoietic Cell Transplantation (HCT)\(^{21}\)
- Lactobacillus plantarum \(1 \times 10^8\) colony-forming units/kg/day
- Examined to ensure they were free of bacteria and fungal contamination
- Pilot study for safety and feasibility of RCT
- Primary objective was safety
- Thirty children and adolescents between 2 and 17 years undergoing HCT
- Started day -8 or -7 through +14
- Ninety-seven percent received at least 50% of dose
- No episodes of lactobacillus bacteremia

Lactobacillus acidophilus Sepsis\(^{22}\)
- Case study
- Sixty-nine year old male with stage IIIA mantle cell lymphoma
- Underwent autologous hematopoietic SCT
- Became septic with Klebsiella pneumonia and was treated for 3 days
- Then developed severe mucositis, vomiting, diarrhea on day 10
- Colonoscopy and biopsy showed chronic inflammation
- Repeated blood cultures that grew Lactobacillus acidophilus
- Eating 6-8 cups/day of probiotic enriched yogurt
- Improved once yogurt was stopped

Febrile Neutropenia

Guidelines
- Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update
- Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America
- Children’s Oncology Group (COG): Guideline for the Management of Fever and Neutropenia in Children with Cancer and/or Undergoing Hematopoietic Stem-Cell Transplantation

Oncologic Fever
- Fever without neutropenia
- Fever with neutropenia
- Fever
  - Temperature > 38.3°C
  - Oral or axillary
  - Avoid rectal – risk of mucosal trauma and bacteremia
  - Neutropenia
  - Mild: ANC 1000 to 1500/microL
  - Moderate: ANC 500 to 1000/microL
  - Severe: ANC < 500/microL

Over the Counter & Supportive Care
- Fever control
  - Acetaminophen (10-15 mg/kg, 5-6 doses/day)
  - Ibuprofen??
- Avoid vaccines at this time
- Avoid fresh flowers
- Daily inspection of vascular site
- Neutropenic diet
- Well-cooked foods
- All people preform hand hygiene
- Daily shower
- Avoidance of tampons
Outpatient Pharmacy Evaluation

- Look at the patient
- Sick vs. non-sick
- Vital signs
- Medical history
- Refer to ED Immediately!!

Inpatient Evaluation

- Vital signs
- Labs
- Cultures
- H&P
- Respiratory virus panel
- C. diff PCR if frequent, watery stools
- Lumbar puncture
- Radiology

Inpatient Empiric Treatment

- Administer antibiotics within 1 hour or sooner
- UNM Hospital
- Ceftriaxone: fever, non-neutropenic
- Cefepime: fever, neutropenic
- Alternatives
- Zosyn, meropenem
- Add vancomycin (q6h dosing) for suspected gram + organism
- Add vancomycin + gentamicin + cefepime for hemodynamic instability

Antibiotic Duration

- De-escalate and treat accordingly to blood cultures
- High risk:
  - Discontinue empiric treatment in patients with neg. blood cultures for 48 hours + afebrile for at least 24 hours + marrow recovery
- Low risk:
  - Discontinue empiric treatment in patients with neg. blood cultures for 48 hours + afebrile for at least 24 hours
- Fungal management for prolonged febrile neutropenia ≥ 96 hours

References

4. Adult Acute Lymphoblastic Leukemia Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute. https://www.cancer.gov/types/leukemia/hp/adult-all-treatment-pdq
5. Adult Acute Myeloid Leukemia Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute. https://www.cancer.gov/types/leukemia/hp/adult-aml-treatment-pdq
6. Neuroblastoma Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute. https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq
References


