Intrathecal Chemotherapy
The ABCs and D.R.P.s

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Objectives
• Review the basics of IT used in pediatric haematology/oncology
• Identify D.R.P.s specific to IT chemotherapy
• Prevent/manage these potential and actual D.R.P.s

Definitions
• AE= adverse event
• ARA-C= cytarabine
• BBB= blood brain barrier
• C1= clearance
• CSF= cerebrospinal fluid
• D.R.P.= drug related problem
• GA= general anaesthetic
• HC= hydrocortisone
• IGT= image guided therapy
• IT= intrathecal chemotherapy
• MDR-1= multi-drug resistant p-170-glycoprotein
• MTX= methotrexate
• M.W.= molecular weight
• LFTs= liver function tests
• LP= lumbar puncture
• PDPH= postdural puncture headache

IT Therapy
• Antineoplastic agents injected directly into the CSF
• Facilitated by LP
  – Also diagnostic
• Same volume of CSF removed as the volume of the IT drug to be administered

Intrathecal Chemotherapy in Children
• Leukemia/lymphoma
  – Prophylaxis
  – Treatment
• Brain tumours
  – Medulloblastoma
Drugs Administered IT

- Anaesthetics
- Analgesics
- Antibiotics
- Adjuvants
- Antineoplastic

IT Agents in Pediatric Haematology/Oncology

- Methotrexate
- Cytarabine
- Corticosteroids
  - Hydrocortisone

Blood Brain Barrier

- Anatomical barrier
  - Endothelial cells connected by tight junctions
  - Fenestrations
  - Astrocytic membrane
- MDR-1
  - Drug efflux pump

Physiochemical Properties

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>ARA-C</th>
<th>HC</th>
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<tbody>
<tr>
<td>M.W.</td>
<td>454.45</td>
<td>243.32</td>
<td>484.52</td>
</tr>
<tr>
<td>Ionized at physiological pH</td>
<td>Weak acid</td>
<td>Weak acid</td>
<td>Weak base</td>
</tr>
<tr>
<td>Protein binding</td>
<td>50%</td>
<td>13%</td>
<td>90%</td>
</tr>
<tr>
<td>Solubility</td>
<td>H₂O Soluble</td>
<td>Moderately H₂O Soluble</td>
<td>Slightly soluble in H₂O</td>
</tr>
<tr>
<td>MDR-1</td>
<td>Actively transported (short term exposure)</td>
<td>Not a substrate</td>
<td>Substrate</td>
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CSF

- Flows at 25mL/hr within ventricles
- Volume of children after age 3 is equivalent to adults
- IT produces more consistent drug levels
  - Volume difference of blood: CSF = 3500ml:140mL
- T1/2 of drugs in CSF>plasma
  - CI mechanism is bulk flow
  - Negligible metabolism/protein binding
**Pharmacokinetics of IT Methotrexate**
- Elimination from CSF
  - Biphasic curve, T1/2 of 4.5h and 14h
- Slow diffusion into plasma
- Potential for prolonged systemic exposure/toxicity
  - Caution special populations (Trisomy 21)

**Pharmacokinetics of IT ARA-C**
- Elimination from CSF
  - Biphasic, T1/2 of 1h and 3.4h
  - Metabolized very slowly to ARA-U (inactive compound) in CSF
    - Negligible presence of enzyme cytidine deaminase in brain/CSF compared to plasma
- Cl from CSF 8x longer than plasma
  - Single IT dose may provide 24h therapeutic level

**Pharmacokinetics of IT Hydrocortisone**
- Limited data

**IT Administration**

**IT Administration: SickKids Policy**
- Patient must have platelet count of 50x10^9/L
- Given with patient under deep sedation in CUJO’s room or under GA in the OR or IGT
- By H/O Staff MD, H/O fellows, CNS/NPs under a medical directive
- Double check of IT drugs by 2 staff
- No other antineoplastic for IV/PO/IM in room

**IT Administration: SickKids Procedure**
- Perform lumbar puncture
- Remove same volume of CSF as IT agent to be administered
- Inject IT agent once CSF is flowing freely
- Place patient in supine position for ≥1h to facilitate even distribution throughout CSF
IT Administration: BC Cancer Agency Policy and Procedure
- Double check system
  - MD to read label aloud
- Only drugs permitted in treatment area are IT chemotherapy and drugs for analgesia and sedation
- Chemotherapy administered over 1-2mins

Search Strategy
- Medline
  - MeSH heading
    - Spinal injection, spinal puncture, headache, postdural puncture headache, antineoplastic agent, methotrexate, cytarabine, steroids
  - Keywords
    - Intrathecal, triple intrathecal therapy
- Pharmacy Drug Information File
  - Administration, Intrathecal

Prevention of Procedure Related D.R.P.s
- Pre-procedural platelet count
  - 20x10^9/L minimum
- Procedural sedation
- Administration procedure
  - 22 gauge needle used on 8A
  - Performed by experienced staff
  - Angle of bevel to entry point
- Pain management
  - Systemic opioids

IT D.R.P.s: Identification, Prevention, Management

POSTDURAL PUNCTURE HEADACHE
- Onset 48h post-procedure
- Duration (untreated) days to months
- Exacerbated by being upright, relieved by lying down
- Associated symptoms
  - nausea, hearing loss, vertigo, dizziness, visual disturbances, cranial palsies
- Mechanism
  - CSF loss through the dural defect created by the LP needle
  - Volume difference of withdrawal/injection
**PDPH**

- **Risk Factors**
  - Age
    - Highest incidence in age 18-29 (16%)
      - May use larger (20-gauge needle, increased reporting)
      - Decreases with increasing age
    - Children 3-17 years old, incidence reported as 8% with a 22-gauge needle (Ramamoorthy et al.)
  - Bevel orientation
  - History of previous PDPH

**PDPH Management**

- Bed rest/rehydration – no benefit
- Supportive therapy – limited benefit
  - Acetaminophen, opioids, NSAIDS, antiemetics
- Posture – prone position advocated
  - May be uncomfortable
- Abdominal binder
  - Increases intra-abdominal pressure
  - May be uncomfortable

**NAUSEA/VOMITING**

- SickKids formulary rank IT therapy as moderately emetogenic (2)
  - Ondansetron 5mg/m² pre-IT and then Q12H
  - Evidence based

**IT D.R.P.s:**

- **Drug Specific**
  - Dosing
  - Systemic toxicity
    - Drug interactions
  - Methotrexate-IT
  - Cytarabine-IT
  - Hydrocortisone-IT
IT D.R.P.s: Dosing

- Age-related dosing vs. Weight/BSA
  - Older children
    - Lower incidence of neurotoxicity
  - Younger children
    - Lower rate of CNS relapse in patients with ALL

MTX-IT: Adverse Effects

Neurotoxicity

- Acute (most common)
  - Hours-days post administration
  - Vomiting, headache, nuchal rigidity, fever, CSF pleocytosis
- Subacute
  - 2-3 weeks post administration
  - Paralysis of limbs or cranial nerve palsy

MTX-IT: Adverse Effects

Neurotoxicity

- Delayed
  - Months-years post administration
  - Related to total drug exposure + cranial irradiation
  - Progressive demyelinating leukoencephalopathy, limb spasticity, dementia, coma
- IT MTX toxicity can lead to death

MTX Systemic AE

- Haematologic effects
- Mucositis
- Nausea/vomiting
- Hepatotoxicity
- Renal toxicity
- Osteonecrosis, myopathy

MTX AE Management

- Prophylactic leucovorin for high risk groups
- For systemic toxicity
  - Increased hydration
  - Leucovorin as per protocol
  - Caution possible drug interactions
- For IT toxicity (limited efficacy)
  - Intrathecal instillation of carboxypeptidase G2
  - Systemic high dose leucovorin
  - CSF drainage
- Monitor
  - Renal function, creatinine, urine output, mucositis, blood counts, LFTs

ARA-C - IT: Adverse Effects

- Seizures
- Transient paraplegia
- Peripheral neuropathy
- Acute arachnoiditis
ARA-C Systemic AE
- Haematological effects
- Fever
- Rash
- Nausea/Vomiting
- Bowel necrosis
- Visual disturbances (high dose)

ARA-C AE Management
- Monitor
  - Rash, fever, blood counts, visual changes
- Symptom management

HC- IT: Adverse Effects
- Sterile abscess
- Aseptic Meningitis
- Opportunistic infections

HC Systemic AE
- Na/fluid retention
- Hypertension
- Nausea/abdominal pain
- Hyperglycemia
- Opportunistic infections

HC AE Management
- Monitor
  - Fluid balance, Na, BP, glucose
- Symptom management

Summary
- D.R.P.s secondary to the LP-IT administration procedure
  - Proper administration procedure is key
- Pharmacists Role:
  - Prophylactic antiemetics
  - Pain management
  - Monitoring/treatment of PDPH
Summary

- D.R.P.s secondary to IT drug therapy
- Pharmacist Role:
  - Monitoring for IT-related and systemic toxicity
  - Leucovorin/hydration for MTX
  - Symptom management

References