CHILLS & THRILLS: IATROGENIC CLOZAPINE TOXICITY

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Clozapine

- Atypical antipsychotic
- Tricyclic dibenzodiazepine derivative
- Indication: refractory schizophrenia
- Restricted use & registry
- Special dosing regimen
- Dose: 200-900mg/day
Clozapine: pharmacology

1. Dopamine – D₁, D₂ & D₄
2. Serotonin – 5-HT₁C & 5-HT₂A
3. Adrenergic – α₁ & α₂
4. Muscarinic – M₁
5. Histamine – H₁
6. ?GABA_A blockade
Dosing, Monitoring, Restricting

- National registries
- Restricted clozapine prescribers
- Special starting guide
- Monitoring regime
- Cessation and re-challenge protocols

### Recommended CLOZARIL® (clozapine) dosage titration at start of therapy

<table>
<thead>
<tr>
<th>Week 1</th>
<th>am (mg)</th>
<th>hs (mg)</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5-25</td>
</tr>
<tr>
<td>Day 2</td>
<td>25</td>
<td>–</td>
<td>25</td>
</tr>
<tr>
<td>Day 3</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Day 4</td>
<td>25</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>Day 5</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Day 6</td>
<td>50</td>
<td>75</td>
<td>125</td>
</tr>
<tr>
<td>Day 7</td>
<td>50</td>
<td>100</td>
<td>150</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 2</th>
<th>am (mg)</th>
<th>hs (mg)</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 8</td>
<td>50</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>Day 9</td>
<td>100</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Day 10</td>
<td>100</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Day 11</td>
<td>50</td>
<td>200</td>
<td>250</td>
</tr>
<tr>
<td>Day 12</td>
<td>50</td>
<td>200</td>
<td>250</td>
</tr>
<tr>
<td>Day 13</td>
<td>100</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>Day 14</td>
<td>100</td>
<td>200</td>
<td>300</td>
</tr>
</tbody>
</table>

*After May 12, 2005 values for WBC and ANC counts requiring increased monitoring frequency of therapy*
Clozapine toxicity

- Agranulocytosis
- CNS: sedation, delirium, seizures
- Autonomic:
  - Anti-muscarinic toxicity
  - Sialorrhea
- Neuromuscular: akathisia, myoclonus, NMS
- Clozapine fever
- Cardiovascular toxicity
- Sudden death
Focus: Clozapine

1. Fever

2. Cardiac:
   - Orthostatic hypotension & tachycardia
   - Myocarditis
   - Cardiomyopathy
   - Pericarditis
   - ?QT prolongation?

3. Sudden Death
Clozapine fever

- Common in initial 4 weeks (0.5%-50%)
  - Systematic retrospective study (HKG): 14% *
- Risk factors
  - Rate of titration
  - Physical illness
  - Valproate therapy
- Differential Diagnosis
  - Infection/sepsis
  - NMS
- Pathophysiology
  - Cytokines (TNF-α, IL-6, GCSF)

* Chung. Can J Psych 2008
Clozapine cardiac disease

- First attention late 1990s
- Kilian, Celermajer et al, Lancet 1999:
  - 15 cases of myocarditis
  - 8 cases of cardiomyopathy
  - amongst 8000 patients & reported to ADRAC

- What’s so special about CLOZAPINE?
## Epidemiology

<table>
<thead>
<tr>
<th>Myocarditis – Absolute risk comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (ADRAC) ^</td>
</tr>
<tr>
<td>UK #</td>
</tr>
<tr>
<td>US FDA *</td>
</tr>
</tbody>
</table>

# UK Committee on Safety of Medicines. *Curr Prob Pharmacovigilance* 1993  
### In Australia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis</td>
<td>0.7 - 1.2%</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Pathophysiology

- IgE-mediated hypersensitivity reaction
  - Eosinophilia
  - Endomyocardial eosinophilic inclusions
- Others
  - Inflammatory cytokines
  - Low selenium

### 1. Presenting features of adverse reactions to clozapine and of biopsy-proven idiopathic myocarditis

<table>
<thead>
<tr>
<th>Clozapine adverse drug reactions cited by researchers, in order of frequency&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Presenting features in patients with biopsy-proven idiopathic myocarditis&lt;sup&gt;13&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electro- or echocardiographic abnormality (66%)</td>
<td>Abnormal ECG in all patients (prolonged QT interval in 90%)</td>
</tr>
<tr>
<td>Fever (49%)</td>
<td>Dyspnoea (90%)</td>
</tr>
<tr>
<td>Tachycardia (46%)</td>
<td>Palpitations/arrhythmia (70%)</td>
</tr>
<tr>
<td>Elevated troponin level (36%)</td>
<td>Elevated levels of cardiac biomarkers (70%)</td>
</tr>
<tr>
<td>Chest pain (32%)</td>
<td>Influenza-type illness/viral prodrome (including fever) (50%)</td>
</tr>
<tr>
<td>Elevated creatine kinase level (31%)</td>
<td>Tachycardia (40%)</td>
</tr>
<tr>
<td>Leucocytosis (28%)</td>
<td>Leucocytosis (35%)</td>
</tr>
<tr>
<td>Dyspnoea (27%)</td>
<td>Chest pain (25%)</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram.

Investigations

- CRP: non-specific but earliest marker

- Troponin I/T: Low sensitivity but high specificity

- NT-proBNP
  - Raised in cardiac failure but also acute myocarditis
  - 2 small series show significant increase and resolution with treatment of clozapine-induced myocarditis

- Eosinophilia: variably reliable

- CK not useful
Investigations

- ECG: 66% non-specific ECG abnormalities

- Echocardiogram
  - Non-specific findings e.g. segmental/global wall motion abnormalities, increased sphericity/LV vol.

- cMRI: Growing body of data in acute myocarditis

- Endomyocardial biopsy
  - Risky, low sensitivity, conflict with interpretation
Management

- Withhold/cease clozapine
- Supportive treatment based on morbidity
- Ongoing monitoring:
  - BP @ 6w, 18w, q6M
  - ECG @ 6M, q1Y
  - ECHO @ 6M, PRN
  - Troponin & CRP: pre, 1-4w, 6w, 18w, 6M, q6M
  - CK-MB & NT-proBNP when myocarditis suspected
- Corticosteroids
- Re-challenge regimes
Sudden death

- Sudden death rate ~4x higher for clozapine #
- Potentially due to:
  - Cardiac arrhythmias: QT prolongation
  - Underlying cardiac disease
  - Clozapine-induced cardiac complications
  - Pulmonary embolus
  - Agranulocytosis/sepsis
- Significant QT prolongation rare *

* Warner. ADR Tox Reviews 2002
Recap on Clozapine

• Restrictive and specialized

• Wide-ranging iatrogenenic potential
  • Agranulocytosis
  • Clozapine fever
  • Anti-cholinergic toxicity
  • NMS
  • Cardiac toxicity
  • Sudden death