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. GABAₐ blockade
Dosing, Monitoring, Restricting

- National registries (US/UK/Aust. since 1990)
- Restricted clozapine prescribers
- Special starting guide
- Monitoring regime
- Cessation and re-challenge protocols

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**Clozapine toxicity**

- Agranulocytosis 1-2%
- CNS: sedation, delirium, seizures
- Autonomic:
  - Anti-muscarinic toxicity
  - Sialorrhea
- Neuromuscular: akathisia, myoclonus, NMS
- Clozapine fever
- Cardiovascular toxicity
- Sudden death

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**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 (KKG): 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 Psychiatry 2008

Clozapine cardiac disease

- First attention late 1990s
- Kilian, Celemajer 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>
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<tbody>
<tr>
<td>Australia (ADRAC) *</td>
</tr>
<tr>
<td>UK #</td>
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<tr>
<td>US FDA *</td>
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In Australia

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

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

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

<table>
<thead>
<tr>
<th>Presenting features</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Electrocardiographic abnormality (64%)</td>
<td>90%</td>
</tr>
<tr>
<td>Fever (5%)</td>
<td>80%</td>
</tr>
<tr>
<td>Tachycardia (64%)</td>
<td>Palpitations/arrhythmia (5%)</td>
</tr>
<tr>
<td>Elevated troponin level (3%)</td>
<td>Elevated levels of cardiac troponins (5%)</td>
</tr>
<tr>
<td>Chest pain (31%)</td>
<td>Influenza-like illness/irritable proctome (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 (33%)</td>
</tr>
<tr>
<td>Dypnoea (27%)</td>
<td>Chest pain (25%)</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram

Clozapine-induced myocarditis

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: Q/T prolongation
  - Underlying cardiac disease
  - Clozapine-induced cardiac complications
  - Pulmonary embolus
  - Agranulocytosis/sepsis
- Significant QT prolongation rare *

* Warner. ADR Tox Reviews 2002