Clozapine: Treat the Patient or Treat the Level?

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## Treat the Level, not the Patient

<table>
<thead>
<tr>
<th>Indication for TDM</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug not working as expected (poor adherence, inadequate dose?)</td>
<td>Any</td>
</tr>
<tr>
<td>Well-defined target range, response difficult to assess clinically</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>‘Toxic concentration’ associated with latent toxicity</td>
<td>Lithium, ciclosporin, sirolimus, everolimus</td>
</tr>
<tr>
<td>‘Therapeutic’ dose associated with severe toxicity in naïve subject</td>
<td>Clozapine</td>
</tr>
</tbody>
</table>
Clozapine

- Effective drug, but very toxic unless used carefully
- Extremely dangerous in clozapine-naïve subject (cautious dose titration)
- Idiosyncratic toxicity (bone marrow, heart, liver, etc.)
- Narrow range of plasma concentrations associated with efficacy/minimal risk of dose-related toxicity (hyper-salivation, drowsiness, convulsions, constipation, etc.)
- Eliminated by hepatic metabolism: dose requirement varies dramatically depending on smoking habit (CYP1A2), other drugs, etc.
- No plasma clozapine monitoring, no clozapine
Why Clozapine TDM?

• As with all TDM, need a reason for doing the test

• Clozapine not working as expected
  – Adherence/dose inadequate?
  – Augment?

• Dose too high?
  – Is an AE c/o likely due to clozapine?
  – Is clozapine psychotic at higher doses/plasma concentrations?

• Should I be adjusting the dose because my patient has started/stopped smoking?
Clozapine TDM: Interpretation

< 0.35 mg/L: Possible reason for poor/no response

0.35–0.6 mg/L: Best response/minimal AEs

(Lower limit may be 0.2 mg/L once control achieved/in elderly patients)

0.6–1 mg/L: Cautious dose reduction (may lose response)?

(aim to bring below 1 mg/L before augmenting)

> 1 mg/L: Cautious dose reduction (anticonvulsant cover?)

> 2 mg/L: URGENT dose reduction (anticonvulsant cover?)
Summary TDM Data 1993-2007
(N = 104,127 from 26,796 patients)

<table>
<thead>
<tr>
<th></th>
<th>Plasma concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Clozapine</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>1,534*</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Samples from 1259 patients; in 247 of these samples norclozapine detected at low concentration (0.05 mg/L or less)
No Clozapine Detected 1993-2007: Dose (N = 998)
Inquest Told of Death at Hospital

Oxford Mail Tuesday 13 January 2009

• A patient found collapsed in a hospital bathroom may have taken a fellow patient’s drugs, an inquest heard today

• Tests after his death found a potentially fatal amount of clozapine, a drug he had never been prescribed

• Post mortem femoral blood clozapine and norclozapine concentrations were 0.48 and 0.20 mg/L, respectively

• A fellow patient admitted later on the day he died that he had shared his drugs with him
Clozapine Pk - Practicalities

- Up to 50 x inter-individual variation in metabolic rate
- Very few serious drug-drug interactions
  - Fluvoxamine, some antibiotics (erythromycin, ciprofloxacin), carbamazepine, phenytoin
  - Other SSRIs little/no effect
- Smoking habit big effect (dose requirement ± 50 % on average smokers/non-smokers)
- Clozapine clearance dose dependent (first pass saturable?)
  - Basis of cautious dose titration
  - Basis of clozapine accumulation in some patients
Norclozapine (N-Desmethylclozapine)

- Main plasma clozapine metabolite
- Has longer plasma half-life than clozapine
- More may accumulate in tissue (possibly even in brain) than clozapine
- May have antipsychotic activity (has similar in vitro receptor binding & white cell toxicity to clozapine)
- Plasma C:NC ratio (early samples sent to us) averaged 1.33 across dose range (50–900+ mg/d)
  - C:NC ratio as important as dose and smoking status in determining plasma clozapine
The young male smoker with TRS

[Graph showing data for Clozapine, Norclozapine, Dose, and Target for clozapine over time from 06/03 to 06/04.]
Why Measure Norclozapine?

• Ensure selective assay used (important for PM work)
• Helps assess adherence (less short-term change than clozapine)
• C:NC ratio (inbuilt QA)
  < 0.5 suggests poor adherence in preceding day(s)
  > 3 suggests not ‘trough’ sample (or inhibition of N-demethylation)
  BUT ratio saturable (normally more obvious if plasma clozapine > 1 mg/L)
# Plasma Clozapine/Norclozapine vs. Dose

(Median, 10th & 90th percentiles, mg/L; N = 85,958)

<table>
<thead>
<tr>
<th>Dose (mg/d)</th>
<th>N</th>
<th>Clozapine</th>
<th>Norclopzidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-150</td>
<td>2,632</td>
<td>0.20 (0.06-0.55)</td>
<td>0.13 (0.05-0.28)</td>
</tr>
<tr>
<td>151-250</td>
<td>8,338</td>
<td>0.30 (0.09-0.72)</td>
<td>0.19 (0.08-0.38)</td>
</tr>
<tr>
<td>251-350</td>
<td>18,794</td>
<td>0.34 (0.13-0.79)</td>
<td>0.23 (0.10-0.46)</td>
</tr>
<tr>
<td>351-450</td>
<td>20,677</td>
<td>0.40 (0.16-0.90)</td>
<td>0.27 (0.12-0.53)</td>
</tr>
<tr>
<td>451-550</td>
<td>14,504</td>
<td>0.45 (0.19-1.00)</td>
<td>0.31 (0.15-0.60)</td>
</tr>
<tr>
<td>551-650</td>
<td>10,509</td>
<td>0.50 (0.22-1.08)</td>
<td>0.35 (0.16-0.67)</td>
</tr>
<tr>
<td>651-750</td>
<td>5,507</td>
<td>0.54 (0.23-1.16)</td>
<td>0.37 (0.18-0.72)</td>
</tr>
<tr>
<td>751-850</td>
<td>3,129</td>
<td>0.57 (0.25-1.25)</td>
<td>0.39 (0.19-0.80)</td>
</tr>
<tr>
<td>851-</td>
<td>1,868</td>
<td>0.55 (0.25-1.24)</td>
<td>0.41 (0.19-0.84)</td>
</tr>
</tbody>
</table>
Plasma Clozapine/Norclozapine vs. Dose
(median, 10th & 90th percentiles; N = 85,958)

- Clozapine
- Norclozapine
- Target for clozapine

[Graph showing the relationship between prescribed dose (mg/d) and plasma levels of clozapine and norclozapine, with target levels indicated.]
Clozapine ≥ 2 mg/L 1993-2007
(N = 461,379 patients)

8 samples (7 patients) co-prescribed omeprazole, 7 (4 patients) co-prescribed fluvoxamine, 1 sample from patient co-prescribed erythromycin)
# Clozapine TDM 1993-2003: Summary

<table>
<thead>
<tr>
<th>Plasma clozapine (mg/L)</th>
<th>&lt;0.01</th>
<th>&lt;0.35</th>
<th>0.35–</th>
<th>0.60–</th>
<th>1.0–</th>
<th>2.0–</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M</strong> (41,878 samples, 12,228 patients)</td>
<td>N 679*</td>
<td>18,855</td>
<td>12,050</td>
<td>7,434</td>
<td>2,745</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>% 1.6</td>
<td><strong>45.0</strong></td>
<td><strong>28.8</strong></td>
<td>17.8</td>
<td>6.6</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>F</strong> (16,294 samples, 5,143 patients)</td>
<td>N 214**</td>
<td>5,814</td>
<td>4,598</td>
<td>3,702</td>
<td>1,835</td>
<td>131</td>
</tr>
<tr>
<td></td>
<td>% 1.3</td>
<td>35.7</td>
<td>28.2</td>
<td><strong>22.7</strong></td>
<td><strong>11.3</strong></td>
<td><strong>0.8</strong></td>
</tr>
</tbody>
</table>

* 566 patients  ** 178 patients
A Female Non-smoker with TRS

Also prescribed aripiprazole, C:NC median 3.0 (range 2.5–3.9)
Clozapine TDM Data 1993-2003
(N = 58,497)

Where information available:

- Males significantly younger (p < 0.01): mean age males 36 yr, females 39 yr
- Males significantly heavier (p < 0.01): mean male weight 86 kg, female 79 kg
- Smoking habit: 71 % of males smokers, 59 % of females
Clozapine 1993-2003: Dose
(Median, 10–90\textsuperscript{th} percentile, N = 32,082)

- Male
- Female

### Smoker
- Median: 17,620 mg/d
- 10–90\textsuperscript{th} percentile: 5,576 mg/d

### Non-Smoker
- Median: 5,996 mg/d
- 10–90\textsuperscript{th} percentile: 3,290 mg/d

(p < 0.01)
Clozapine 1993-2003: Plasma Clozapine
(Median, 10–90th percentile, N = 34,530)

![Graph showing plasma clozapine levels for male and female smokers and non-smokers.](image)

- Male smokers: Median = 0.4 mg/L (17,742), 10–90th percentile = 0.2–0.6 mg/L
- Female smokers: Median = 0.8 mg/L (3,930), 10–90th percentile = 0.4–1.4 mg/L
- Male non-smokers: Median = 0.6 mg/L (5,662), 10–90th percentile = 0.4–0.8 mg/L
- Female non-smokers: Median = 1.2 mg/L (7,195), 10–90th percentile = 0.4–1.6 mg/L

Significant difference between smokers and non-smokers (p < 0.01) for both male and female.
Clozapine TDM: Summary

- **Treat the level:**
  - If nothing there!
  - If > 2 mg/L!

- **Treat the level AND the patient**
  - If poor adherence/too low a dose confirmed (< 0.35 mg/L)
  - If AE likely related to level (usually >0.5 mg/L)
  - If >1 mg/L attempt cautious dose reduction even if good response and no AEs

- **Treat the patient (taking into account the level)**
  - If 0.35–0.6 mg/L, no AEs, good response – leave alone!
  - If >0.6 mg/L, no AEs, good response – it depends…
  - If augmentation considered, bring level < 1 mg/L before adding new drug
Further Reading


• MacCall CA, et al. Clozapine: More than 900 mg/d may be needed. J Psychopharmacol 2008 23; 206-10


More Reading


• Couchman L, et al. Plasma clozapine and norclozapine in patients prescribed different brands of clozapine (Clozaril®, Denzapine®, and Zaponex®). *Ther Drug Monit* 2010; 32: 624-7
