Chapter 1

Plasma level monitoring of psychotropic drugs and anticonvulsants

Plasma drug concentration or plasma 'level' monitoring is a process surrounded by some confusion and misunderstanding. Drug level monitoring, when appropriately used, is of considerable help in optimising treatment and assuring adherence. However, in psychiatry, as in other areas of medicine, plasma level determinations are frequently undertaken without good cause and results acted upon inappropriately. Conversely, in other instances, plasma concentrations are underused.

Before taking a blood sample for plasma level assay, check the following.

- **Is there a clinically useful assay method available?** Only a minority of drugs have available assays. The assay must be clinically validated and results available within a clinically useful timescale.
- **Is the drug at 'steady state'?** Plasma levels are usually meaningful only when samples are taken after steady-state levels have been achieved. This takes 4–5 drug half-lives.
- **Is the timing of the sample correct?** Sampling time is vitally important for many but not all drugs. If the recommended sampling time is, say, 12 h post dose, then the sample should be taken 11–13 h post dose if possible; 10–14 h post dose, if absolutely necessary. For trough or 'predose' samples, take the blood sample immediately before the next dose is due. Do not, under any circumstances, withhold the next dose for more than 1 or (possibly) 2 h until a sample is taken. Withholding for longer than this will inevitably give a misleading result (it will give a lower result than ever seen in the usual, regular dosing), which may lead to an inappropriate dose increase. Sampling time is less critical with drugs with a long half-life.
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(e.g. olanzapine) but, as an absolute minimum, prescribers should always record the time of sampling and time of last dose.

If a sample is not taken within 1–2 h of the required time, it has the potential to mislead rather than inform. The only exception to this is if toxicity is suspected – sampling at the time of suspected toxicity is obviously appropriate.

■ Will the level have any inherent meaning? Is there a target range of plasma levels? If so, then plasma levels (from samples taken at the right time) will usefully guide dosing. If there is not an accepted target range, plasma levels can only indicate adherence or potential toxicity. If the sample is being used to check compliance, bear in mind that a plasma level of zero indicates only that the drug has not been taken in the past several days. Plasma levels above zero may indicate erratic compliance, full compliance or even long-standing non-compliance disguised by recent taking of prescribed doses. Note also that target ranges have their limitations: patients may respond to lower levels than the quoted range and tolerate levels above the range; also, ranges quoted by different laboratories sometimes vary widely without explanation.

■ Is there a clear reason for plasma level determination? Only the following reasons are valid:
  – to confirm compliance (but see above)
  – if toxicity is suspected
  – if a pharmacokinetic drug interaction is suspected
  – if clinical response is difficult to assess directly (and where a target range of plasma levels has been established)
  – if the drug has a narrow therapeutic index and toxicity concerns are considerable.

Interpreting sample results

The basic rule for sample level interpretation is to act upon assay results in conjunction with reliable clinical observation (‘treat the patient, not the level’). For example, if a patient is responding adequately to a drug but has a plasma level below the accepted target range, then the dose should not normally be increased. If a patient has intolerable adverse effects but a plasma level within the target range, then a dose decrease may be appropriate.

Where a plasma level result is substantially different from previous results, a repeat sample is usually advised. Check dose, timing of dose and recent compliance but ensure, in particular, the correct timing of the sample. Many anomalous results are the consequence of changes in sample timing.

Table 1.1 shows the target ranges for some commonly prescribed psychotropic drugs.
Table 1.1 Interpreting plasma concentration sample results for psychotropic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target range</th>
<th>Sample timing</th>
<th>Time to steady state</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>200–320 µg/l</td>
<td>Trough</td>
<td>3 days</td>
<td>See text</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>150–210 µg/l</td>
<td>Trough</td>
<td>15–16 days</td>
<td>See text</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>&gt; 7 mg/l bipolar disorder</td>
<td>Trough</td>
<td>2 weeks</td>
<td>Indicates its own metabolism. Time to steady state dependent on autoinduction</td>
</tr>
<tr>
<td>Clozapine</td>
<td>350–500 µg/l</td>
<td>Trough (12 h post-dose if once daily)</td>
<td>2–3 days</td>
<td>See text</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Not established but suggest 2.5–15 mg/l</td>
<td>Trough</td>
<td>5 days</td>
<td>Some debate over utility of lamotrigine levels, especially in bipolar disorder. Toxicity may be increased above 15 mg/l</td>
</tr>
<tr>
<td>Lithium</td>
<td>0.6–1.0 mmol/l (may be &gt;1.0 mmol/l in mania)</td>
<td>12 h post dose</td>
<td>3–5 days</td>
<td>Well-established target range</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20–40 µg/l</td>
<td>12 h</td>
<td>1 week</td>
<td>See text</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>20–60 µg/l (9-OH risperidone)</td>
<td>Trough</td>
<td>2–3 days oral 2 months depot</td>
<td>No obvious reason to suspect range should be any different from risperidone. Some practical confirmation</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10–20 mg/l</td>
<td>Trough</td>
<td>Variable</td>
<td>Follows zero-order kinetics. Free levels may be useful</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Around 50–100 µg/l?</td>
<td>Trough?</td>
<td>2–3 days oral</td>
<td>Target range not defined. Plasma level monitoring not recommended. See text</td>
</tr>
</tbody>
</table>

(Continued)
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Table 1.1 (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target range</th>
<th>Sample timing</th>
<th>Time to steady state</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>20–60 μg/l</td>
<td>Trough</td>
<td>2–3 days oral, 6–8 weeks injection</td>
<td>Plasma level monitoring is not recommended. See text</td>
</tr>
<tr>
<td></td>
<td>(active moiety – risperidone + 9-OH risperidone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Nortriptyline 50–150 μg/l</td>
<td>Trough</td>
<td>2–3 days</td>
<td>Rarely used and of dubious benefit. Use ECG to assess toxicity</td>
</tr>
<tr>
<td></td>
<td>Amitriptyline 100–200 μg/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>50–100 mg/l</td>
<td>Trough (if once daily at night, sample at 12–24 h)</td>
<td>2–3 days</td>
<td>Some doubt over value of levels in epilepsy and in bipolar disorder. Some evidence that levels up to 125 mg/l are tolerated and more effective than lower levels (in mania)</td>
</tr>
<tr>
<td></td>
<td>Epilepsy and bipolar</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECG, electrocardiogram.

Amisulpride

Amisulpride plasma levels are closely related to dose with insufficient variation to recommend routine plasma level monitoring. Higher levels observed in women\(^{18-20}\) and older patients\(^{18,20}\) seem to have little significant clinical implication for either therapeutic response or adverse effects. A (trough) threshold for clinical response has been suggested to be approximately 100 μg/l\(^{21}\), mean levels of 367 μg/l\(^{20}\) have been noted in responders in individual studies. Adverse effects (notably extrapyramidal side-effects [EPS]) have been observed at mean levels of 336 μg/l\(^{18}\), 377 μg/l\(^{21}\) and 395 μg/l\(^{19}\). A plasma level threshold of below 320 μg/l has been found to predict avoidance of EPS\(^{21}\). A review of the current literature\(^{22}\) has suggested an approximate range of 200–320 μg/l for optimal clinical response and avoidance of adverse effects.

In practice, amisulpride plasma level monitoring is rarely undertaken and few laboratories offer amisulpride assays. The dose–response relationship is sufficiently robust to obviate the need for plasma sampling within the licensed dose range; adverse effects are well managed by dose adjustment alone. Plasma level monitoring is best reserved for those in whom clinical response is poor, adherence is questioned and in whom drug interactions or physical illness may make adverse effects more likely.
Aripiprazole

Plasma level monitoring of aripiprazole is rarely carried out in practice. The dose–response relationship of aripiprazole is well established, with a plateau in clinical response and D2 dopamine occupancy seen at doses above approximately 10 mg/day.\textsuperscript{23} Plasma levels of aripiprazole, its metabolite and the total moiety (parent plus metabolite) strongly relate linearly to dose, making it possible to predict, with some certainty, an approximate plasma level for a given dose.\textsuperscript{24} Target plasma level ranges for optimal clinical response have been suggested as 146–254 µg/l\textsuperscript{25} and 150–300 µg/l,\textsuperscript{26} with adverse effects observed above 210 µg/l.\textsuperscript{26} Interindividual variation in aripiprazole plasma levels has been observed but not fully investigated, although gender appears to have little influence.\textsuperscript{27, 28} Age, metabolic enzyme genotype and interacting medications seem likely causes of variation\textsuperscript{26–29} but there are too few reports regarding their clinical implication to recommend specific monitoring in respect to factors. A putative range of 150–210 µg/l\textsuperscript{24} has been suggested as a target for patients taking aripiprazole who are showing little or no clinical response or who have intolerable EPS. For reasons described here, plasma level monitoring is not advised in routine practice.

Clozapine

Clozapine plasma levels are broadly related to daily dose\textsuperscript{30} but there is sufficient variation to make any precise prediction of plasma level impossible. Plasma levels are generally lower in younger patients, males\textsuperscript{31} and smokers\textsuperscript{32} and higher in Asians.\textsuperscript{33} A series of algorithms has been developed for the approximate prediction of clozapine levels according to patient factors and these are strongly recommended.\textsuperscript{34} Algorithms cannot, however, account for other influences on clozapine plasma levels such as changes in adherence, inflammation\textsuperscript{35} and infection.\textsuperscript{36} The plasma level threshold for acute response to clozapine has been suggested to be 200 µg/l,\textsuperscript{37} 350 µg/l,\textsuperscript{38–40} 370 µg/l,\textsuperscript{41} 420 µg/l,\textsuperscript{42} 504 µg/l\textsuperscript{13} and 550 µg/l.\textsuperscript{44} Limited data suggest that a level of at least 200 µg/l is required to prevent relapse.\textsuperscript{35} Substantial variation in clozapine plasma level may also predict relapse.\textsuperscript{46} Despite these varied estimates of response threshold, plasma levels can be useful in optimising treatment. In those not responding to clozapine, dose should be adjusted to give plasma levels in the range 350–500 µg/l. Those not tolerating clozapine may benefit from a reduction to a dose giving plasma levels in this range. An upper limit to the clozapine target range has not been defined. Plasma levels do seem to predict electroencephalogram (EEG) changes\textsuperscript{47, 48} and seizures occur more frequently in patients with levels above 1000 µg/l\textsuperscript{49} so levels should probably be kept well below this. Other non-neurological clozapine-related adverse effects also seem to be related to plasma-level,\textsuperscript{50} as might be expected. Note that clozapine metabolism may become saturated at higher doses: the ratio of clozapine to norclozapine increases with increasing plasma levels, suggesting saturation.\textsuperscript{51–53} The effect of fluvoxamine also suggests that metabolism via CYP1A2 to norclozapine can be overwhelmed.\textsuperscript{54} Placing an upper limit on the target range for clozapine levels may discourage potentially worthwhile dose increases within the licensed dose range. Before plasma levels were widely used, clozapine was fairly often given in doses up to 900 mg/day, with valproate being added.
when the dose reached 600 mg/day. It remains unclear whether using these high doses can benefit patients with plasma levels already above the accepted threshold. Nonetheless, it is prudent to use an anticonvulsant as prophylaxis against seizures and myoclonus when plasma levels are above 500–600 μg/l and certainly when levels approach 1000 μg/l.

Olanzapine

Plasma levels of olanzapine are linearly related to daily dose, but there is substantial variation, with higher levels seen in women, non-smokers and those on enzyme-inhibiting drugs. With once-daily dosing, the threshold level for response in schizophrenia has been suggested to be 9.3 μg/l (trough sample), 23.2 μg/l (12-h postdose sample) and 23 μg/l at a mean of 13.5 h post dose. There is evidence to suggest that levels greater than around 40 μg/l (12-h sampling) produce no further therapeutic benefit than lower levels. Severe toxicity is uncommon but may be associated with levels above 100 μg/l, and death is occasionally seen at levels above 160 μg/l (albeit when other drugs or physical factors are relevant). A target range for therapeutic use of 20–40 μg/l (12-h postdose sample) has been proposed for schizophrenia; the range for mania is probably similar.

Significant weight gain seems most likely to occur in those with plasma levels above 20 μg/l. Constipation, dry mouth and tachycardia also seem to be related to plasma level.

In practice, the dose of olanzapine should be governed by response and tolerability. Plasma level determinations should be reserved for those suspected of non-adherence or those not responding to the maximum licensed dose (at 20 mg/day, around 20% of patients will have olanzapine levels <20 μg/l). In the latter case, dose may then be adjusted to give 12-h plasma levels of 20–40 μg/l.

Quetiapine (IR)

Dose of quetiapine is weakly related to trough plasma concentration. Mean levels reported within the dose range 150 mg/day to 800 mg/day range from 27 μg/l to 387 μg/l, although the highest and lowest levels are not necessarily found at the lowest and highest doses. Age, gender and co-medication may contribute to the significant interindividual variance observed in therapeutic drug monitoring studies, with female gender, older age and CYP3A4-inhibiting drugs likely to increase quetiapine concentration. Reports of these effects are conflicting and not sufficient to support the routine use of plasma level monitoring based on these factors alone. Thresholds for clinical response have been proposed as 77 μg/l and 50–100 μg/l. EPS has been observed in females with levels in excess of 210 μg/l. Despite the substantial variation in plasma levels at each dose, there is insufficient evidence to suggest a target therapeutic range, so plasma level monitoring has little value.

Most current reports of quetiapine concentrations are from trough samples. Because of the short half-life of quetiapine, trough levels tend to drop to within a relatively small range regardless of dose and previous peak level. Thus peak plasma levels may be more closely related to dose and clinical response although monitoring of such is not currently justified in the absence of an established peak plasma target range. Quetiapine has an established
Plasma level monitoring

dose–response relationship and appears to be well tolerated at doses well beyond the licensed
dose range. In practice, dose adjustment should be based on patient response and tolerability.

Risperidone

Risperidone plasma levels are rarely measured in the UK and very few laboratories have de-
veloped assay methods for its determination. Plasma level monitoring is probably unproductive
(dose–response is well described) except where compliance is in doubt and in such cases,
measurement of prolactin will give some idea of compliance.

The therapeutic range for risperidone is generally agreed to be 20–60 \( \mu \text{g/l} \) of the active
moiety (risperidone + 9-OH risperidone)\(^{60,81}\) although other ranges (25–150 \( \mu \text{g/l} \) and
25–80 \( \mu \text{g/l} \)) have been proposed.\(^82\) Plasma levels of 20–60 \( \mu \text{g/l} \) are usually afforded by oral
doses of between 3 mg and 6 mg a day.\(^{80,83–85}\) Occupancy of striatal dopamine D\(_2\) receptors
has been shown to be around 65% (the minimum required for therapeutic effect) at plasma
levels of approximately 20 \( \mu \text{g/l} \).\(^81\)

Risperidone long-acting injection (25 mg/2 weeks) appears to result in plasma levels aver-
aging between 4.4 and 22.7 \( \mu \text{g/l} \).\(^84\) Dopamine D\(_2\) occupancies at this dose have been variously
estimated at between 25% and 71%.\(^81,86,87\) There is considerable interindividual variation
around these mean values, with a substantial minority of patients with plasma levels above
those shown. Nonetheless, these data do cast doubt on the efficacy of a dose of 25 mg/2 weeks\(^84\)
although it is noteworthy that there is some evidence that long-acting preparations are effective
despite apparently subtherapeutic plasma levels and dopamine occupancies.\(^88\)

References

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