

The use of clozapine plasma levels in optimising therapy

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Clozapine is well known to be an effective treatment for neuroleptic-resistant schizophrenia. However, its use is complicated by a variable and delayed response and by a range of troublesome adverse effects. Current practice is usually to increase the dose initially to around 450 mg/day and then by small increments to a maximum of 900 mg/day according to response and tolerability. While this method is often successful, it has been suggested that a better way of optimising the dose of clozapine might be to monitor plasma concentrations of the drug.

If plasma levels are to be useful, they must be difficult to predict simply from the dose given to an individual patient. In an early study, Thorup & Fog (1977) investigated the variation in serum levels both between individuals on the same dose and within individuals. In the eleven patients studied, the dose given seemed to have little bearing on the measured plasma level and levels varied widely in some patients despite a constant dose. This latter anomaly may have been due to changes in intestinal absorption or to erratic compliance. The assay method also appeared to be somewhat inaccurate: a level of 31 ng/ml was measured in a control patient not taking clozapine. Using a different assay method, Bondesson & Lindstrom (1988) examined levels in 22 patients and found that dose correlated well with resultant plasma level. Parent drug levels were also well correlated with clozapine's major metabolite norclozapine. A much larger study (Haring *et al.*, 1989) of 148 patients again showed a significant but weak ($r=0.5266$) correlation between dose and serum level. Further analysis revealed that male patients and smokers had significantly lower levels than females and non-smokers respectively. Older patients had higher levels. Haring *et al.* (1990), apparently reporting the same study ($n=148$) with different co-authors and a different analysis of results, established a linear relationship ($r=0.61$) between dose and serum

level. Variation in the relationship was, unsurprisingly, mostly accounted for by age (levels lower in younger patients), smoking (lower in smokers) and gender (lower in males).

Thus, there appears to be a weak but definite relationship between the dose of clozapine and the plasma level which results. Plasma concentrations tend to be lower in younger patients, in males and in smokers. Because of the generally weak correlation between dose and level and the range of influencing factors, it would seem difficult to predict with any precision the plasma level which might be afforded by a given dose. Moreover, clozapine plasma levels appear to be readily altered by the co-administration of other drugs: carbamazepine reduces clozapine levels (Raitasuo *et al.*, 1993) and fluoxetine may greatly increase them (Centorrino *et al.*, 1994).

Given that the plasma level cannot accurately be predicted from the dose, it is important to establish whether levels relate to efficacy or to the severity of adverse effects. In Thorup & Fog's small study there was no correlation between plasma level and therapeutic effect. In a later and larger study of 29 patients, Perry *et al.* (1991) established a threshold for response to clozapine of 350 ng/ml. Below this level 22% responded, but above it 64% responded. (The overall low response rate of 37.9% was due to the short (4–8 weeks) trial period.) A follow-up study of the same patients two and a half years later showed that overall response rate had risen to 58% (Miller *et al.*, 1994). Five of seven non-responders from the first study became responders after obtaining a level higher than 350 ng/ml. Piscitelli *et al.* (1994), in a six week trial, compared serum levels to response in eleven adolescents with schizophrenia. A consistent linear relationship between level and response was discovered although no threshold level was established. In a four week study of 48 adult schizophrenics (Potkin *et al.*, 1994), the threshold level for response was found to be 420 ng/ml – 60% of

patients with levels above this responded compared with 8% for those with levels below it. Increasing levels in non-responders above 420 ng/ml greatly improved response. Interestingly, clozapine levels varied 45-fold in patients given the same dose. In the most recent study, Kronig *et al* (1995) studied clozapine levels in 45 patients given large doses of clozapine for six weeks. No correlation between plasma level and response could be found but a threshold of 350 ng/ml was established for response after six weeks of treatment.

One long-term study (Hasegawa *et al*, 1993) investigated the relationship between response and serum clozapine levels. Fifty-nine treatment-resistant patients given clozapine for up to 76 months had random clozapine and norclozapine levels taken. Response to clozapine (defined as 20% Brief Psychiatric Rating Scale reduction) was said to have occurred in 30 patients at six months. In these, the dose of clozapine was not significantly different to the dose in non-responders but serum levels of clozapine and norclozapine were significantly higher. A clozapine serum level of 370 ng/ml was said to be the optimum cut-off point to distinguish responders from non-responders although six of the non-responders had levels above this value and 14 responders had levels below it. Another interesting finding was that clozapine serum levels did not differ between male smokers and non-smokers.

Plasma clozapine levels appear also to relate to adverse effects. Simpson & Cooper (1978) described two cases of seizures occurring in patients with high levels of clozapine. One had no seizures while maintaining a level of 600 ng/ml but suffered a grand mal seizure when the level rose to 1313 ng/ml following an overdose. Another suffered a grand mal seizure after a drug administration error resulted in a clozapine serum level of 2194 ng/ml. Kane *et al* (1981) discovered that high clozapine levels appeared to be related to lower prolactin levels in two schizophrenic patients given clozapine for up to 15 weeks, although changes in prolactin levels were small. In another tentative study ($n=60$) (Pollack *et al*, 1993), it was found that clozapine-induced tardive dyskinesia (an effect now known to be very rare) was significantly associated with higher clozapine plasma levels (above around 500 ng/ml).

Higher clozapine levels also appear to be associated with pathological electroencephalogram (EEG) changes. Haring *et al* (1993) found that 15 patients showing EEG changes

had a mean clozapine plasma level of 235.7 ng/ml whereas those with a normal EEG ($n=14$) had a mean level of only 81.6 ng/ml. Perhaps the most important adverse effect of clozapine is neutropenia; Centorrino *et al* (1995) found that there was no association between the degree of leucopenia caused by clozapine and clozapine or norclozapine plasma levels.

Clozapine serum levels are difficult to predict from the dose given and there are many factors which influence the serum level obtained. Short- and long-term studies have shown that the minimum effective concentration is probably between 350–420 ng/ml and that there may be a linear relationship between plasma level and response, at least in adolescents. Some of clozapine's adverse effects also appear to be plasma level related; EEG changes and seizures seem particularly sensitive to rises in serum levels.

In conclusion, clozapine plasma levels can be said to be useful in optimising therapy. A 'therapeutic range' of serum levels has not yet been established but, based on the evidence presented here, it seems wise to recommend that prescribers aim initially for a dose of 450 mg/day and, if there is no response after six weeks, serum levels should be measured¹, and the dose adjusted so that a level of at least 350 ng/ml is obtained. Levels substantially higher than this should be approached very cautiously. Prescribers should expect to give higher doses to young patients, males and smokers.

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1. 'Trough' samples should be drawn immediately before the next dose is due to be given. In cases of unequal dosing, take the sample twelve (BD dosing) or eight hours (TDS) after the largest of the doses.

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Treatment of psychotropic-induced hyperprolactinaemia

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Prolactin, a protein hormone synthesised and released by the anterior pituitary, promotes mammary tissue development and lactation and suppresses gonadotrophin secretion. Dopamine is the natural inhibitor of prolactin release and so standard antipsychotics, which block dopamine receptors, will cause prolactin levels to rise. This hyperprolactinaemia can lead to gynaecomastia, galactorrhoea, menstrual disturbances, a reduction in sperm count, erectile dysfunction, failure of ejaculation and reduced libido. Prolactin-related adverse effects are frequently encountered in patients on antipsychotics and are a cause of substantial morbidity.

All antipsychotics except clozapine are associated with hyperprolactinaemia. In the majority of cases the rise in prolactin levels causes few problems. If, however, troublesome adverse effects occur, prolactin serum levels may be reduced by decreasing the dose of antipsychotic or discontinuing treatment. If this is not practicable, limited trial work has supported the use of amantadine or bromocriptine. This is reviewed below.

Amantadine's mechanism of action remains unclear but it is thought to enhance dopaminergic activity by causing a release of dopamine or by direct agonist activity. Because amantadine had been used successfully to treat