10 - Olanzapine

Olanzapine

Pharmacokinetics CHAPTER 11 an individual’s clozapine plasma levels are common with a tendency for concentrations to slightly decrease over time,72 although one study suggests a decrease only in norclozapine concentrations.73 Despite these somewhat varied estimates of response threshold, plasma levels can be useful in optimising treatment. In those not responding to clozapine, the dose should be adjusted to give plasma levels in the range 350–600mcg/L (a range reflecting a consensus of the above findings32). 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. Any upper limit must take into account two components: the level above which no therapeutic advantage is gained and the level at which toxicity/ tolerability is unacceptable. Plasma levels do seem to predict EEG changes74,75 and seizures occur more frequently in patients with levels above 1000mcg/L,76 so levels should probably be kept well below this. Other non-neurological clozapine-related adverse effects also seem to be plasma-level related77 as might be expected. An upper limit of concentrations around 600–800mcg/L has been proposed,78 although a level of 1000mcg/L may be the point of futility.79,80 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 sometimes given in doses up to 900mg/day, with valproate being added when the dose reached 600mg/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 antiseizure agent as prophylaxis against seizures and myoclonus when plasma levels are above 600mcg/L (a level based more on repeated recommendation than on being a clear evidence-based threshold78) and certainly when levels approach 1000µmcg/L. Norclozapine is the major metabolite of clozapine. The ratio of clozapine to norclozapine averages 1.25 in populations81 but may differ markedly for individuals.82 In chronic dosing, the ratio should remain the same for a given patient. A decrease in ratio may suggest enzyme induction, an increase suggests enzyme inhibition, a non-trough sample or recent missed doses. Time of sampling radically alters the clozapine/norclozapine ratio as clozapine is relatively high in early samples and norclozapine is higher in late samples.1 Clozapine metabolism may become saturated at higher doses: the ratio of clozapine to norclozapine increases with increasing plasma levels, suggesting saturation.83–85 The effect of fluvoxamine also suggests that metabolism via CYP1A2 to norclozapine can be overwhelmed.86 Ultimately, changes in the clozapine/norclozapine ratio may be impossible to interpret. A systematic review concluded that knowledge of clozapine/norclozapine ratio had no clinical utility.87 Olanzapine Plasma levels of olanzapine are linearly related to daily dose88 but there is substantial variation,89 with higher levels seen in women,68 non-smokers90 and those on enzyme-inhibiting drugs.90,91 With once-daily dosing, the threshold level for response in schizophrenia

has been suggested to be 9.3mcg/L (trough sample),92 23.2mcg/L (12-hour post-dose sample)68 and 23mcg/L at a mean of 13.5 hours post-dose.93 There is evidence to suggest that levels greater than around 40mcg/L (12-hour sampling) produce no

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