

Clozapine drug levels guide dosing

Oliver Freudenreich, MD

Once you have an accurate drug level, take advantage of clozapine's linear pharmacokinetics; if you double the dose, you double the level

Finding the best clozapine dosage for your psychotic patient can be challenging because any given dose of the drug yields highly variable clozapine serum levels. This interindividual variability reflects clozapine's complex metabolism.

Obtaining serum levels will help you determine if your patient remains psychotic because of insufficient dosing or if your asymptomatic patient can safely receive a lower dose to minimize side effects without risking psychotic relapse. Following these guidelines will help you make the best use of clozapine drug levels.

Obtaining clozapine levels

Measure clozapine as steady-state trough levels. I usually draw them 12 hours after the last dose (such as in the morning after the nightly dose) and several days after treatment begins.

When you order a clozapine level, most laboratories report 3 numbers: clozapine, norclozapine, and their sum. The literature addresses only the clinical use of clozapine levels and ignores the much less active metabolite, norclozapine.

Interpreting clozapine levels

Although there is no simple relationship among clozapine levels, therapeutic efficacy, and toxicity, a randomized clinical trial of patients with chronic schizophrenia¹ compared 3 non-overlapping ranges and found:

- "medium" range (200 to 300 ng/mL) is a good initial target
- low range (50 to 150 ng/mL) is not as effective as medium or high levels
- high range (350 to 450 ng/mL) can be tried if clinical response is insufficient, although the high range was no more effective than the medium range
- very high levels (ie >1,000 ng/mL combined clozapine and norclozapine levels) have no proven benefit and increase seizure risk.

These guidelines are based on bid or tid dosing. If your patient receives clozapine only at night, take into account the higher morning level compared with the same dose administered on a split schedule.

Adjusting clozapine dose

Now that you have an accurate drug level, take advantage of clozapine's linear pharmacokinetics. If you double the dose, you double the level; if you halve the dose, you halve the level.

For example, consider the case of a schizophrenia patient who remains psychotic despite a clozapine dose of 200 mg bid (400 mg/d). His clozapine level is 100 ng/mL (ie, low range) and his norclozapine level is 50 ng/mL. This patient would need double his dose (800 mg/d) to achieve a clozapine level at the low end of the medium range (200 ng/mL). Note that the norclozapine level is ignored for this calculation.

Reference

1. VanderZwaag C, McGee M, McEvoy JP, et al. Response of patients with treatment-refractory schizophrenia to clozapine within three serum level ranges. *Am J Psychiatry*. 1996;153:1579-1584.

Dr. Freudenreich is director, Massachusetts General Hospital's first episode and early psychosis program, Boston.

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