Clozapine

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Various toxicities: case report

A 46-year-old man developed sweating, pale face, blue lips, ataxia, tremors in the arms and legs, unsteadiness on feet, lethargy, echolalia, loss of initiative, fatigue, drowsiness, tiredness and reduced alertness during treatment with clozapine for schizophrenia [*route and duration of treatment to reactions onsets not stated*].

The non-smoker man had a severe intellectual disability of unknown cause and was living at an institution for people with intellectual disabilities. He had been receiving clozapine 200mg twice daily for schizophrenia. At steady state, the clozapine trough level was 553 µg/L, the clozapine level/dose (C/D) ratio was 1.4, and the clozapine/norclozapine (C/N) ratio 1.7. His medical history was remarkable for several infections, including one episode of bacterial pneumonia, two episodes of bronchitis and an infection of the upper respiratory tract. During bronchitis episodes and the upper respiratory tract infection, the clozapine level did not increase beyond 661 µg/L (C/D ratio, 1.7). During bacterial pneumonia, the clozapine level elevated to 1183 µg/L (C/D ratio, 2.4). On several occasions, including during bacterial pneumonia, halving the dosage of clozapine led to psychotic decompensation. In April 2020, during the COVID-19 pandemic, he tested positive for COVID-19. Home quarantine measure was taken. At that time, clozapine trough level was 553 µg/L, the clozapine level/dose (C/D) ratio was 1.4, and the clozapine/norclozapine (C/N) ratio was 1.8. From day 4 onward, he became increasingly ill. He developed sweating, pale face, blue lips, ataxia, tremors in the arms and legs and unsteadiness on feet. These symptoms were considered secondary to clozapine intoxication. Subsequently, he was admitted. His treatment was started with oxygen and paracetamol for fever.

Due to the history of psychotic decompensation after the man's clozapine dosage was halved during fever, from day 4 onward he received the clozapine dose on the basis of whether his temperature was ≥38°C. If the temperature was ≥38°C, the dosage was reduced to 300 mg/day (on days 4, 5 and 7) divided over two doses (8 a.m., 8 p.m.). On day 6 the dose was increased back to 400 mg/day. During days 4–6, he was lethargic with sweating, echolalia, loss of initiative and increased fatigue, which were attributed to clozapine intoxication. His temperature fluctuated between 37.1°C and 38.7°C. On day 7, his condition deteriorated further with temperature of 39.4°C. Due to the suspicion of bacterial pneumonia in addition to COVID-19, he was initiated on amoxicillin/clavulanic-acid. His home medications included atenolol, diazepam, esomeprazole and lithium. At that time, the clozapine trough levels were three times as high as usual: 1814 µg/L. The C/D ratio was 5, which was calculated using the mean dosage over the past 5 days. The C/N ratio was 3.5. At that point, clozapine was stopped. From day 9 onward, he started to recover with clozapine level of 1335 µg/L.

The man's clozapine treatment was re-started with 25 mg/day from day 10 onward, after 48 hours of the clozapine discontinuation. After re-initiation, the clozapine dose was cautiously titrated. On day 13, he received clozapine 50 mg/day, (clozapine level, 213 µg/L). On day 19, he received clozapine 100 mg/day (clozapine level, 107 µg/L). However, during days 12–14, he was drowsy, tired with fatigue and had reduced alertness. These symptoms were attributed to clozapine intoxication. Thereafter, on day 23 he showed clinical improvement. On days 30 and 37, the serum clozapine levels, C/D and C/N ratios were normal, and he had recovered clinically. Following recovery the clozapine dose was increased to 350 mg/day. He was discharged to home quarantine, with clozapine titration schedule to usual dose of 400 mg/day.

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