The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Elevated clozapine plasma concentration secondary to a urinary tract infection: proposed mechanisms

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A 59-year-old woman was admitted to a tertiary care refractory psychosis unit with a referral diagnosis of schizoaffective disorder. She was maintained on 400 mg of clozapine once daily as part of her pre-existing treatment for auditory hallucinations. The steady state plasma concentrations of clozapine and norclozapine were 2542 and 1465 nmol/L, respectively (metabolic ratio: 1.74). Seven weeks later, the plasma concentrations of clozapine and norclozapine increased to 3272 and 2025 nmol/L, respectively (metabolic ratio: 1.62), despite no changes in medications (including doses), smoking status, or adherence (based on previous clozapine levels). Although no adverse effects were observed in association with the elevated plasma concentrations, the daily dose was reduced to 200 mg as a precautionary measure. Upon investigation, a urinary tract infection (UTI) was diagnosed, for which nitrofurantoin and cotrimoxazole were initiated. After 1 week of antibiotic therapy, clozapine and norclozapine plasma concentrations decreased to 1406 and 639 nmol/L, respectively (metabolic ratio: 2.20).

Similar increases in the plasma concentrations of clozapine and norclozapine have been described in other case reports involving concurrent UTIs.[1–5] Adverse effects attributed to elevated plasma concentrations of clozapine include somnolence, confusion, disorientation, dizziness, aphasia and extrapyramidal symptoms.[1–5] Apart from UTIs, this phenomenon has also been reported in association with other infectious processes and with tissue injury,[1,6–9] sometimes without clozapine-associated adverse effects.[10] The mechanism implicated in increasing plasma concentrations of clozapine and norclozapine is not believed to be related to the exposure to the pathogen or the damage to the tissue, but rather the effects of cytokines released in response to proinflammatory events, such as those mentioned above.[11]

Several cytokines involved in the acute inflammatory response have been identified as having an inhibitory effect on the expression of certain drug metabolizing enzymes. For instance, a downregulation of cytochrome P450 (CYP) 1A2 and CYP3A messenger RNA has been reported following the incubation of human hepatocytes with tumour necrosis factor, interleukin (IL)-1β, and IL-6. Furthermore, the activity of these enzymes were also reduced by the same cytokines.[12] Since clozapine is primarily metabolized by CYP1A2, with contributions from CYP3A4,[13] reductions in their expression and activity offer an explanation to the noted increase in its plasma concentration. However, this mechanism may not be in operation in our patient since the clozapine/norclozapine metabolic ratios did not increase from baseline to the time of UTI diagnosis. Typically, the ratio would increase to a value greater than 2:1 in response to inhibition of CYP1A2. Interestingly, there was a modest increase in the clozapine/norclozapine metabolic ratio after treatment for the UTI, which is consistent with the inhibitory effect of cotrimoxazole on CYP2C9, an enzyme involved in the demethylation of clozapine to norclozapine.[14]

A second mechanism that has been proposed to explain the UTI-associated elevations in the plasma concentrations of clozapine and norclozapine is related to an increase in α1-acid glycoprotein,[10] an acute-phase protein whose synthesis is upregulated by cytokines such as IL-6.[15] An increase in α1-acid glycoprotein will increase the binding capacity of both clozapine and norclozapine. The outcome will be an increase in the total (bound and unbound) plasma concentrations of clozapine and norclozapine; however, the unbound (free and active moiety) concentrations will remain unchanged. Since clinical laboratories report only total (bound and unbound) plasma concentrations, confirmation that the free levels have remained unchanged is not possible. The fact that the patient did not exhibit any clozapine-associated adverse effects supports the supposition that the free concentrations did not increase despite the increase in total concentration. Measuring plasma concentrations of α1-acid glycoprotein (if available) would have helped to confirm this proposed mechanism.

UTI-associated increases in the plasma concentrations of clozapine and norclozapine are most readily explained by the actions of cytokines on drug metabolism and/or protein binding. Since we could not readily order plasma concentrations of unbound clozapine or α1-acid glycoprotein, confirmation of the underlying mechanism(s) was not possible. As such, clinicians should monitor for clozapine-associated adverse effects and adjust the dosage accordingly.

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