

Infection-Associated Clozapine Toxicity

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Abstract

Three case vignettes are presented documenting the rise in serum clozapine that occurred at a time of acute infection in these patients. The literature on this phenomenon is scant. The physiological processes that occur in the acute phase of the inflammatory response are summarized and provide an explanation of how clozapine levels may rise in response to infection. The risk of clozapine toxicity occurring in association with infections is highlighted.

Key Words: Clozapine, Infection, Toxicity

Introduction

We report clozapine toxicity developing in three non-smokers during acute infections. We discuss the association between the inflammatory response and clozapine toxicity.

Taylor et al. reported the deaths of five people taking clozapine from pneumonia (1) and their commentary on this highlighted the complex relationship between clozapine and infection, and the potential for infection to lead to toxic levels of serum clozapine (2).

Case Reports

Case #1

A 42-year-old man with Schizophrenia, who was a non-smoker treated with clozapine 300 mg daily for 4 months (serum clozapine level 1,509 nmol/L [1,000–2,000]), presented with insomnia, pyrexia and a productive cough of sudden onset. In addition to the clozapine, he was prescribed citalopram 20 mg daily, benzotropine 2 mg daily and clonazepam 0.25 mg daily. His white blood cell count was 14.3 (4–11). Amoxicillin was prescribed for an upper respiratory tract infection. Two days later he became disorganized, disoriented, confused, and had

difficulty expressing himself. He was producing copious amounts of purulent sputum. His serum clozapine level was 5,307 nmol/L, C-reactive protein 116 mg/L (0–7), erythrocyte sedimentation rate 48 mm/hr (0–23) and white blood cell count 13.1. Clozapine was stopped and his cognitive symptoms resolved within 48 hours. Clozapine was then restarted at a dose of 100 mg daily with a serum level of 547 nmol/L after 5 days. Over the following month, his dose was gradually increased to 300 mg daily with no problems.

Case #2

A 50-year-old woman (nonsmoker) with Schizoaffective Disorder taking 300 mg clozapine daily (plus sodium valproate 500 mg twice daily, benzotropine 2 mg twice daily, metoprolol CR 95 mg twice daily, bendrofluazide 2.5 mg daily and felodipine ER 10 mg daily) presented with sudden onset drowsiness, slurred speech, shortness of breath, an unproductive cough and urinary incontinence. Previous baseline serum clozapine levels were not available and her serum clozapine level was 7,950 nmol/L. Her white blood cell count was 10.9, with a neutrophil count of 9.36 (2–7.5). The clozapine was stopped, and trimethoprim prescribed for a presumed urinary tract infection. The other medications were continued. Two days later, a chest x-ray showed patchy opacities throughout both lungs with bilateral small pleural effusions. She commenced amoxicillin clavulanate and her condition improved. Over the next 6 days, her clozapine level dropped to 368 nmol/L, with resolution of her drowsiness, speech disturbance and urinary incontinence. Clozapine was restarted after 2 weeks with no difficulty and, at 3 weeks, her serum level was 545 nmol/L on a dose of 75 mg daily.

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Case #3

A 45-year-old woman (nonsmoker) with Schizophrenia had been treated with clozapine for 8 years and was taking 700 mg daily. She was also prescribed sodium valproate 1 gram twice daily. Her most recent serum clozapine level was 1,550 nmol/L. She presented with urinary frequency, dysuria, and with an elevated white blood cell count of 22.4, with a neutrophil count of 17.02 (2–7.5). She was prescribed trimethoprim. Her condition deteriorated, and two days later she was admitted to hospital with dizziness and an unstable gait. *E coli* was cultured in her urine and her white blood cell count had increased to 26.94; serum C-reactive protein was 237 mg/L (3–5 mg/L), and her serum clozapine level was 14,505 nmol/L. Clozapine was stopped, and over the following 10 days the serum level dropped to 627 nmol/L, with resolution of her neurological symptoms. Clozapine was restarted and increased to 500 mg, giving a serum level of 1,941 nmol/L after 3 months.

Discussion

Clozapine is oxidatively metabolized in hepatocytes by the cytochrome P450 system, with about 70% being metabolized by CYP1A2 (the remaining 30% is metabolized by various other CYP450 enzymes) (3, 4). Drugs inhibiting this system, which increase serum clozapine levels, include omeprazole, theophylline, modafinil and fluvoxamine. Caffeine is a substrate of CYP1A2 and can also increase clozapine levels. Smoking and carbamazepine are CYP1A2 inducers and reduce clozapine levels. Smoking cessation or stopping carbamazepine can cause clozapine toxicity unless the dose of clozapine is reduced (5).

During the acute phase of inflammation, the cytochrome P450 enzymes, including CYP1A2, are down regulated by up to 90% with the cytokine interleukin 6 (IL6) being the most important factor in this process (6). Macrophages and neutrophils are stimulated to produce pro-inflammatory cytokines (like IL1, TNF, IL8, and interferon) which stimulate the synthesis of second-phase cytokines (like IL6) which are then disseminated into the blood. In the liver, IL6 stimulates hepatocytes to synthesize and secrete acute phase proteins like C-reactive protein.

These patients presented with symptoms suggestive of clozapine toxicity in the context of acute infections. Their elevated serum levels of clozapine were consistent with the expected inhibition of their metabolic pathways by inflammatory factors, particularly IL6. It raises the interesting question of how often a rise in clozapine goes unrecognized during infections and how tolerant individuals are to such elevated levels of clozapine (7).

Clozapine toxicity has been documented largely in the context of acute overdose. The manufacturer (Novartis) reports a dose-related mortality which reaches 12% with

overdoses above 2,500 mg (8). Symptoms are consistent with the receptor profile of the drug (i.e., serotonergic, anticholinergic, antiadrenergic, and antihistaminic). In the above case reports these included drowsiness, lethargy, confusion, agitation, tachycardia, hypotension and respiratory depression.

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It is well known that clozapine reduces the seizure threshold in a dose-dependent manner. It is of interest that none of our patients experienced seizures. This may be because patients 2 and 3 were taking sodium valproate concurrently.

Patients taking clozapine who develop acute infections may develop toxic levels of clozapine as its metabolism is impaired by the acute inflammatory response (9, 10). Patients should be observed closely for signs of such toxicity, and their clozapine reduced or stopped and serum levels monitored. Similar caution should be exercised in other clinical conditions where the acute inflammatory response is triggered and IL6 elevated, such as acute trauma.

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