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Infection and Inflammation Leading to Clozapine Toxicity and Intensive Care: A Case Series

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Infection and inflammation leading to clozapine toxicity and intensive care: a case series

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| Keywords: | Schizophrenia, Psychiatry, Psychotropics, Antipsychotics (Atypical), Toxicity |
| Abstract: | <p>Objective: To describe 3 cases of clozapine toxicity associated with infectious and/or inflammatory processes.</p> <p>Case Summaries: 3 patients stable on clozapine therapy prior to a medical hospital admission developed clozapine toxicity. It was suspected that an acute infectious and/or inflammatory process in each patient was related to abrupt mental status changes, onset of sialorrhea, myoclonus, and/or need for ventilatory support. Investigations of altered mental status did not reveal alternative causes and presentations were not consistent with neuroleptic malignant syndrome, other acute neurologic complications, or psychiatric decompensation. All patients improved after clozapine dose reductions allowing for transfer from intensive care units. Using the Naranjo ADR Probability Scale for each case, a probable relation between clozapine toxicity and the infectious and/or inflammatory process was determined.</p> <p>Discussion: Clozapine toxicity may manifest with multiple symptoms including sedation, sialorrhea, and hypotension. In addition to overdose and drug interactions; infection and/or inflammation may precipitate clozapine toxicity. This may be related to cytokine-mediated inhibition of cytochrome P450 1A2. The likelihood of toxicity via this mechanism has not been well-characterized, thus careful monitoring is required for medically ill patient receiving clozapine. Clozapine is extensively bound to the acute phase reactant, alpha-1 acid glycoprotein, which may unpredictably protect against clinical toxicity. C-reactive protein has also been investigated to relate clozapine toxicity to infection and/or inflammation.</p> <p>Conclusion: Clozapine toxicity developed in 3 patients admitted to a medical setting suspected to be related to infection and/or inflammation. Clinicians should be aware of this potential adverse drug event with clozapine.</p> |

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4 Infection and inflammation leading to clozapine toxicity and intensive care: a case series
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Abstract

Objective: To describe 3 cases of clozapine toxicity associated with infectious and/or inflammatory processes.

Case Summaries: 3 patients stable on clozapine therapy prior to a medical hospital admission developed clozapine toxicity. It was suspected that an acute infectious and/or inflammatory process in each patient was related to abrupt mental status changes, onset of sialorrhea, myoclonus, and/or need for ventilatory support. Investigations of altered mental status did not reveal alternative causes and presentations were not consistent with neuroleptic malignant syndrome, other acute neurologic complications, or psychiatric decompensation. All patients improved after clozapine dose reductions allowing for transfer from intensive care units. Using the Naranjo ADR Probability Scale for each case, a probable relation between clozapine toxicity and the infectious and/or inflammatory process was determined.

Discussion: Clozapine toxicity may manifest with multiple symptoms including sedation, sialorrhea, and hypotension. In addition to overdose and drug interactions; infection and/or inflammation may precipitate clozapine toxicity. This may be related to cytokine-mediated inhibition of cytochrome P450 1A2. The likelihood of toxicity via this mechanism has not been well-characterized, thus careful monitoring is required for medically ill patient receiving clozapine. Clozapine is extensively bound to the acute phase reactant, alpha-1 acid glycoprotein, which may unpredictably protect against clinical toxicity. C-reactive protein has also been investigated to relate clozapine toxicity to infection and/or inflammation.

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5 **Conclusion:** Clozapine toxicity developed in 3 patients admitted to a medical setting
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7 suspected to be related to infection and/or inflammation. Clinicians should be aware of
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9 this potential adverse drug event with clozapine.
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For Peer Review

Introduction

Clozapine is a second generation antipsychotic reserved for the management of treatment resistant schizophrenia. For patients prescribed clozapine admitted to a medical hospital there are important considerations all clinicians should recognize. Upon hospital admission clozapine adherence and dosage must be verified. Due to potent alpha-1 antagonism, if interruption of therapy has been for greater than 48 hours clozapine should be re-titrated to avoid potentially fatal hypotension.¹ Additionally, as clozapine is primarily metabolized via the cytochrome P450 isozyme 1A2 (1A2), knowledge of factors which decrease 1A2 activity is crucial to prevent toxicity. These include smoking cessation and drug interactions. There is also evidence that clozapine toxicity may occur in the setting of an acute infectious and/or inflammatory process as a result of reduced 1A2 activity (Table 1).²⁻⁹ Prior cases describing clozapine toxicity as a result of infectious and/or inflammatory processes have mostly involved respiratory infections; however involvement of gastrointestinal and urinary infections have also been described. Symptoms of toxicity in the reported cases have been generally mild to moderate and included sedation, dizziness and confusion. We report 3 cases in which acute infectious and/or inflammatory processes were believed to have been the inciting factor for clozapine toxicity and the need for intensive care.

Case 1:

A 52 year-old female with chronic obstructive pulmonary disease (COPD), schizophrenia, pulmonary hypertension and coronary artery disease was transferred from an outside facility for management of an acute exacerbation of COPD. Pertinent social

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4 history obtained revealed a smoking history of 3 cigarettes daily. Medications prior to
5 admission included oxybutynin 20 mg, escitalopram 40 mg, aspirin 81 mg,
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8 albuterol/ipratropium, and fluticasone/salmeterol. Upon arrival to an intensive care unit
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10 (ICU) the patient was placed on bilevel positive airway pressure for ventilation (BiPAP)
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12 and treated with albuterol and intravenous steroids. Intravenous azithromycin 500 mg
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16 daily was also initiated although a chest x-ray revealed no evidence of infection. There
17
18 was no fever at the time of admission and pertinent laboratory values from the outside
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20 facility included a white blood cell count (WBC) of 10,400 cells/mm³. Arterial blood
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22 gases obtained before and after placement of BiPAP revealed a resolving respiratory
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25 acidosis, with a pCO₂ of 98 and 80, and pH 7.22 and 7.27, respectively.
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30 Less than 24 hours after admission the patient was transferred to a general
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32 medicine unit. Her clozapine dose (100 mg every morning and 350 mg at bedtime) and
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34 medication adherence were confirmed. Clozapine was restarted after missing 24 hours of
35
36 therapy; and on hospital day 2 she received a bedtime dose and 1 morning dose the
37
38 following day. Prior to the next evening dose the patient was found unresponsive and
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40 required intubation for airway protection. During transfer to the ICU hypotension and
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42 myoclonus were reported. Carbon dioxide retention narcosis was suspected initially,
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44 however a pCO₂ level obtained at the time of decompensation was not significantly
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46 different from her baseline of 55-60 mmHg and pH was appropriately compensated at
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48 7.38. Ammonia was below the level of detection and electrolytes were within normal
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50 limits. Administration of naloxone and flumazenil had no effect on mental status; and an
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52 electroencephalogram was unremarkable. During the initial hours of ICU care, frequent
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54 suctioning was required from newly developed sialorrhea. With myoclonus,
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5 hypotension, sialorrhea and obtundation, clozapine toxicity was suspected. Serum
6
7 clozapine and norclozapine levels obtained 36 hours after the patient's last dose which
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9 were 1400 ng/mL (reference: 350-700 ng/mL) and 606 ng/mL, respectively (ratio 2.3:1).
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11 The patient was seen by neurology and psychiatry consult services who found no
12
13 evidence of serotonin syndrome or neuroleptic malignant syndrome with
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15 recommendations to continue to hold clozapine. The patient was extubated 24 hours after
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17 the episode of unresponsiveness and toxicity resolved over the next several days. After 6
18
19 held doses clozapine and norclozapine serum concentrations were 582 ng/mL and 379
20
21 ng/mL, respectively (ratio 1.5:1). Clozapine was restarted at 50% of the patient's home
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23 dose with further medication adjustments to be completed as an outpatient. Potential
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25 confounders related to this case include a potential interaction between azithromycin and
26
27 clozapine. However, azithromycin is not expected to impact the hepatic metabolism of
28
29 other medications unlike other macrolides.¹¹ Azithromycin has been shown to have no
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31 impact on theophylline pharmacokinetics, which is metabolized similarly as clozapine
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33 (i.e. via 1A2 and 3A4).^{11, 12} It is possible that smoking cessation contributed to toxicity;
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35 but it is unlikely that cessation of 3 daily cigarettes after 48 hours would produce rapid
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37 toxicity requiring intubation. Using the Naranjo ADR Probability Scale¹³ it was
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39 determined that there was a probable relation between the patient's COPD exacerbation
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41 and the onset of clozapine toxicity.
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50 Case 2:
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54 A 49 year-old non-smoking male was admitted for a planned total hip arthroplasty
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56 (THA) for debilitating hip pain. His past medical history was significant for paranoid
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4 schizophrenia and chronic mild renal insufficiency. Six months prior the patient was
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6 hospitalized for a subarachnoid hemorrhage which was complicated by placement of a
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8 ventriculoperitoneal shunt for communicating hydrocephalus. A WBC prior to admission
9
10 was 10.0 cells/mm³ and daily medications included aripiprazole 15 mg, clozapine 400
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12 mg, divalproex sodium 500 mg and escitalopram 10 mg. Prior to the procedure the
13
14 patient was noted to be alert, oriented and in no apparent distress with exception of hip
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16 pain. The THA was completed without complication; however the patient continued to
17
18 be minimally arousable 2 hours after surgery. This was initially thought to be due to
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20 opioid administration during the procedure and in the recovery unit. The patient was
21
22 given repeated boluses of naloxone with minimal effect. Initiation of a naloxone
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24 continuous infusion also had no effect on mental status. The patient required transfer to
25
26 an ICU for observation and was placed on noninvasive ventilation for hypoxemia. A trial
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28 of flumazenil and discontinuation of a psoas nerve block had no effect on sedation. A
29
30 computed tomography scan of the head was negative for any acute process or change
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32 from previous imaging. On hospital day 2, clozapine was decreased to 300 mg daily. A
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34 total valproic acid level was 19 mg/dL (reference: 50-120 mg/dL) and serum ammonia
35
36 was below the detectable level. The patient remained afebrile and there was no
37
38 indication of infectious although WBCs on hospital day 3 and 4 were 14,800 cells/mm³
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40 and 13,000 cells/mm³, respectively. With significant somnolence persisting on hospital
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42 day 4 and new sialorrhea noted, clozapine and norclozapine levels were obtained. Eight
43
44 hours following the last dose, clozapine and norclozapine levels were 1130 ng/dL and
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46 297 ng/dL, respectively (ratio 3.8:1). No further dose adjustments to clozapine were
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48 made and the patient was discharged with gradually resolving somnolence. With the
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5 acute change in mental status post-operative it is possible the patient experienced a
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7 negative reaction to the anesthetic agents utilized. Yet this does not fully explain the
8
9 protracted sedation experienced by the patient plus the new onset of sialorrhea. There
10
11 were also no previous reports of adverse reactions to anesthetics. Vancomycin and
12
13 ceftriaxone were administered pre- and post-operatively which would not interact with
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15 clozapine. There is literature suggesting that divalproex sodium may increase clozapine
16
17 levels; however the patient had been on a stable medication regimen months prior to the
18
19 surgery. The patient did have a complicated neurologic history but no findings were
20
21 found to explain the patient's acute and prolonged sedation or sialorrhea. A
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23 sedimentation rate and C-reactive protein (CRP) were obtained preoperative and were 21
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25 mm/hr (reference range 0-22 mm/hr) and 7.5 mg/L (reference range < 8.0 mg/L),
26
27 respectively suggesting no acute inflammatory process or infection prior to surgery.
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29 Unfortunately these laboratory values were not obtained later during the admission. A
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31 probable relation was determined between the onset of clozapine toxicity and surgical
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33 intervention using the Naranjo ADR Probability Scale.¹³
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41 Case 3:

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44 A 61 year-old female non-smoker was hospitalized for fever after a right hip
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46 fracture requiring surgical intervention twelve days prior. Past medical included arthritis,
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48 schizophrenia, diabetes, hypertension and hypothyroidism. Medications upon admission
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50 from a nursing home included clonazepam 0.5 mg daily, clozapine 100 mg each morning
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52 and 600 mg at bedtime and mirtazapine 7.5 mg at bedtime. Empiric ceftriaxone was
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54 administered for an elevated WBC of 21,600 cells/mm³. She was diagnosed with
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4 pneumonia, urinary tract infection and cellulitis involving the right hip. Antibiotic
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6 therapy was changed to vancomycin and ertapenem for a total of 8 days. After the
7
8 antimicrobial course was completed the patient was taken to the OR on the tenth day of
9
10 admission for a right hip hemiarthroplasty revision. A culture from the hip obtained
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12 during surgery grew extended-spectrum beta-lactamase producing Escherichia coli. The
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14 patient was then continued on ertapenem 1 gram IV daily for 3 additional days post-
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16 operatively. One hospital day twenty-two, the patient developed sepsis with blood
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18 cultures positive for MRSA and vancomycin reinitiation with continued ertapenem. Over
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20 the next 7 days the patient became increasingly somnolent and confused, leading up to a
21
22 non-verbal state. Prior to sepsis she was noted to be psychiatrically stable, mentating
23
24 well with no communication problems. To reduce psychotropic medications, mirtazapine
25
26 was discontinued. Due to ongoing sedation and non-verbal state, on day 38 of
27
28 hospitalization, serum clozapine and norclozapine concentrations drawn prior to the
29
30 morning dose were 4,318 ng/ml and 504 ng/ml, respectively (ratio 8.6:1). The patient's
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32 WBC at this time was 35,700 cells/mm³ with the treatment for sepsis still ongoing.
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34 Clozapine, which had been continued throughout the entire hospitalization, was
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36 decreased to 100 mg nightly and the patient's mental status returned to baseline within 5
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38 days allowing for transfer from the ICU. An aspartate aminotransferase prior to
39
40 obtaining the clozapine level was found to be 53 IU/L (reference: 8-34 IU/L); and while
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42 an alanine transaminase was not available, drug accumulation due to liver dysfunction
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44 was not suspected. There was also no concern for kidney dysfunction throughout
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46 admission.
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5 The acute change in the patient's mental status may have represented the onset of
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7 delirium rather than clozapine toxicity. Critical illness, specifically sepsis in this case,
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9 and the continuation of clonazepam would be considered risk factors for delirium.
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11 Clozapine itself also has also been rarely associated with delirium, believed to be related
12
13 to its anticholinergic properties. However, there was a temporal relation between sepsis
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15 and mental status changes and then clinical improvement after a dose reduction. Other
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17 medications administered during admission, including antibiotics would not have been
18
19 expected to interact with clozapine. It was probable that there was an association
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21 between the newly developed sepsis and clozapine toxicity as determined using the
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23 Naranjo ADR Probability Scale.¹³
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29 Discussion:

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32 These cases highlight the importance of understanding the potential impact of
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34 acute infectious and/or inflammatory processes on clozapine metabolism. While
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36 inhibition of CYP450 pathways is often considered a result of drug-drug interactions,
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38 disease states may also affect these metabolic pathways. In our cases, acute infectious
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40 and/or inflammatory processes were believed to have decreased clozapine metabolism
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42 leading to toxicity identified by both clinical symptoms and serum clozapine levels. In
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44 clinical practice serum levels of 350 ng/mL are generally targeted to maximize clozapine
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46 efficacy with levels greater than 700 ng/mL being associated with increased sedation and
47
48 seizure risk.¹⁴ All patients experienced significant sedation and although none had a
49
50 documented seizure, one patient did develop myoclonus. Myoclonus is a known adverse
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52 event of clozapine which may occur with usual dosing or be an indication of infection.⁷
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4 Sialorrhea which occurs often during the usual course of clozapine treatment may be also
5 explained by acute toxicity and occurred in cases 1 and 2 above.¹⁰ Extensive workup was
6 conducted in all three cases to rule out other causes of mental status changes. The
7 presence for drug interactions was also investigated, noting that previous cases may have
8 been confounded by the use of ciprofloxacin, a strong 1A2 inhibitor. Ciprofloxacin
9 should be avoided if other pharmacologic options are available to avoid significant
10 clozapine-related adverse events.¹⁵

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22 Resolution of the toxicity occurred in a temporal relationship after decreasing or
23 holding clozapine therapy. Striking is that the patient (case 3) with the highest elevations
24 in clozapine levels did not experience the greatest degree of clinical toxicity. This
25 phenomenon has been described by Espnes and colleagues in which a patient with a
26 clozapine level of 9074 nmol/L (2965 ng/mL; conversion factor = 3.06) experienced no
27 clinical toxicity.^{4, 16} This elevation of clozapine levels was suspected to be related to
28 infection with a lack of symptoms due to an increase also of alpha-1 acid glycoprotein
29 (AGP). Human AGP is an acute phase reactant and the primary protein that binds free
30 clozapine. With approximately 97% of clozapine protein bound, as both AGP and serum
31 clozapine levels increase due to infection or inflammation, the net result would not yield
32 an increase of free serum clozapine to produce toxicity.^{1, 4} Interestingly it has been noted
33 that, the acute-phase reaction in response to tissue injury during surgery may be
34 incomplete or absent and AGP levels may not rise, explaining the toxicity seen in case
35 2.¹⁷ As the clinical presentation of the clozapine toxicity varied in all three cases, it is
36 likely that the degree of AGP increased uniquely for each patient. It has also been
37 suggested that CRP may be useful to obtain in patients receiving clozapine. Abou Farha
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4 and colleagues stated that in the setting of suspected clozapine toxicity, infection should
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6 be ruled out as an inciting factor and that CRP is useful to distinguish between overdose
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8 and toxicity related to infection.⁵ Authors also suggest that elevated CRP may be the
9
10 only clinical sign of infection as clozapine may blunt immune mediated increases of
11
12 WBC or development of fever.⁵ Elevated CRP may also be associated with myocarditis
13
14 and benign clozapine-induced fever.¹⁸ Unfortunately during suspected toxicity, AGP and
15
16 CRP laboratory values were not available in our cases.
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22 The suspected mechanism linking clozapine toxicity and acute inflammatory
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24 and/or infectious processes is related to a direct decrease of 1A2 activity. Activity of
25
26 1A2 may be reduced by up to 90% due to increases of IL-6, interferon and TNF- α during
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28 acute infectious and/or inflammatory processes.^{2, 5} Strengthening this hypothesis is the
29
30 fact that patients receiving theophylline, another medication significantly metabolized by
31
32 1A2, are more likely to develop toxicity after the development of respiratory infections.¹⁹
33
34 The degree in which a clozapine dose should be adjusted in the setting of an acute
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36 infectious and/or inflammatory processes is unknown but it has been suggested that at
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38 least a 50% reduction may be necessary to avoid toxicity.²⁰ If doses are reduced there
39
40 should be careful documentation as to the rationale and close patient follow-up after
41
42 resolution of the infection and/or acute inflammatory process. The utility of serum
43
44 clozapine levels to guide dose reductions during acute toxicity may be limited as they are
45
46 often a “send-out” laboratory value. When there is clear evidence of clozapine toxicity
47
48 doses should be reduced with the guidance of psychiatric consultation. However,
49
50 clozapine serum levels may useful to establish a baseline and in a retrospective manner
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52 argue for the case of toxicity when coupled with clinical symptoms. The ideal ratio of
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clozapine to norclozapine is approximately 2:1 and a significantly greater ratio may be indicative of saturated metabolism or 1A2 inhibition.²¹ While clozapine levels are quantifiable it is important that clinicians remember that alarmingly elevated levels may occur without clinical signs of toxicity. In these instances the most appropriate initial action would be to closely monitor for toxicity without a dose reduction and repeat clozapine levels after the acute infectious and/or inflammatory process resolves.

Conclusion:

Three patients developed clozapine toxicity thought to be associated with an acute infectious and/or inflammatory process. Although there were symptoms of toxicity, dose reductions were delayed potentially prolonging the need for ICU care. Patients that develop an acute infectious and/or inflammatory process administered clozapine should be vigilantly monitored for toxicity. Doses should cautiously be adjusted in the setting of significant clozapine toxicity with clinicians remembering serum clozapine levels may not equate to clinical toxicity. Further study is needed to determine the role routine CRP and AGP monitoring.

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Table 1. Additional cases describing clozapine toxicity associated with acute infectious and/or inflammatory processes

| Author (Year, n=) | Pathogenic Process | CLZ Dose/ Range (mg) | CLZ/NCLZ levels (ng/mL) | Management/ Comments |
|---|--|-------------------------|---|---|
| Darling, et al. ² (2011, n=3) | URI, UTI | 300-700 | CLZ mean \pm SD: 3085 + 1579 | - CLZ held; restarted 5-90 days later |
| deLeon, et al. ³ (2003, n=1) | URI | 600 | CLZ: 1245 NCLZ: 472 | - CLZ dose decreased to 400 mg |
| Espnes, et al. ⁴ (2012, n=1) | Bacterial GI infection/ Crohn's colitis | 900 | CLZ: 3024 | - No signs of toxicity - No dose change - Ciprofloxacin prescribed |
| Abou Farha, et al. ⁵ (2012, n=1) | PNA | 300 | CLZ: 1301 NCLZ: 515 | - CLZ stopped due to paralytic ileus |
| Haack, et al. ⁶ (2003, n=4) | PNA, unknown infection, viral illness | 300-600 | CLZ mean + SD: 1872 + 689 NCLZ mean + SD: | - CLZ stopped in all cases |

| | | | | |
|--|-----|-----|----------------------------|---|
| | | | 521 + 190 | |
| Liang, et al. ⁷ (2011, n=1) | PNA | 350 | NR | - Myoclonus and gait instability improved when CLZ decreased to 200 mg - CRP 201, WBC 12,700 |
| Jecel, et al. ⁸ (2005; n=1) | UTI | 200 | CLZ: 1066 NCLZ: 379 | -CLZ decrease to 100 mg and safely increased back to 200 mg after infection resolution - CRP 81.5, WBC 5,500 |
| Raaska, et al. ⁹ (2002, n=1) | PNA | 500 | CLZ: 2074 | Toxicity not reported Dose reduced to 450 mg |

CRP=C-reactive protein, GI = gastrointestinal; PNA = pneumonia; NR = not reported,

URI = upper respiratory infection; UTI = urinary tract infection, WBC= white blood cell

count