mhc MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Clozapine-associated renal failure: A case report and literature review

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How to cite: Davis EAK, Kelly DL. Clozapine-associated renal failure: A case report and literature review. Ment Health Clin [Internet]. 2019;9(3):124-7. DOI: 10.9740/mhc.2019.05.124.

Abstract

One of clozapine's unrecognized potential side effects is renal insufficiency and nephritis. Although most clinicians are aware of the possibility of clozapine-induced myocarditis, less is known about other inflammatory disorders due to clozapine treatment. This patient was started on lithium and clozapine within 4 days of each other although lithium was discontinued after 7 days due to tremor. Routine labs showed an increase in serum creatinine, which was initially attributed to the recent lithium. However, the patient's kidney function continued to worsen, requiring discontinuation of clozapine despite a robust response to a low dose. Several years later, the patient's kidney function improved but has not returned to baseline. This literature review and case report illustrates the similarities in diagnostic presentation of clozapine-associated renal insufficiency as well as potential risk factors. More research should be conducted into the role concomitant sodium valproate and/or lithium play in the risk of clozapine-associated renal insufficiency.

Keywords: clozapine, nephritis, renal failure

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Disclosures: This work was funded in part by NIMH R01MH102215 (D.L.K. as principal investigator). E.A.K.D. has no actual or potential conflicts of interest or financial interests to disclose. D.L.K. serves as an advisor to Lundbeck and HLS Therapeutics.

Background

Clozapine is a second-generation antipsychotic that, despite its efficacy, is reserved for treatment-resistant schizophrenia due to its side effect profile.[1] The most widely known of these side effects is severe neutropenia although others include myocarditis, gastrointestinal hypomotility, pancreatitis, and renal insufficiency. Even though the package insert includes acute interstitial nephritis as a possible side effect, this remains an unrecognized potential hazard of clozapine treatment, and risk factors and diagnostic criteria continue to be unidentified. This case describes the development of renal failure after initiation of clozapine and lithium but that persisted after discontinuation of lithium. We hope this report and review of the literature will help clinicians become more cognizant of this serious complication.

Case Report

A 59-year-old African American male whose current admission has spanned decades was started on clozapine after numerous medication trials. His psychiatric diagnoses included schizophrenia, frotteuristic disorder, obsessive-compulsive disorder, and alcohol and cannabis use disorders in remission in a controlled environment. Past medical history was positive for hypertension, gastroesophageal reflux disorder, anemia, benign ethnic neutropenia, and chronic constipation with no known drug allergies. Laboratory values 4 months prior to the initiation of clozapine were significant for neutropenia, hyponatremia, hypochloremia, and hyperglycemia. Base-

line kidney function tests had been slightly elevated for 4 years and included serum creatinine (SCr) 1.30 mg/dL, blood urea nitrogen (BUN) 11 mg/dL, and estimated glomerular filtration rate (eGFR) 70 mL/min/1.73m^2. Lithium was initiated 4 days prior to the initiation of clozapine but was stopped on day 7 of clozapine therapy due to tremors despite a therapeutic concentration of 0.7 mmol/L. No other renal labs were drawn at this time. Other medications during clozapine initiation included fluoxetine, fluphenazine, quetiapine, amantadine, and divalproex.

Due to the patient's history of chronic constipation, the clozapine dose was very slowly titrated to 50 mg/d by day 21. Even at this low dose, he showed substantial improvement in mood lability and irritability, skin picking, and paper/book hoarding. He no longer endorsed auditory hallucinations, had decreased sexually inappropriate behaviors and comments toward women, reduced paranoia leading to agreement for important medical interventions, and he was able to realistically discuss discharge plans for the first time in years. A basic metabolic panel drawn on day 21 indicated that SCr had increased significantly since baseline (now 2.47 mg/dL) with BUN 24 mg/dL and eGFR 32 mL/min/1.73m^2. Also, he now showed slight eosinophilia with 531 cells/μL. The alterations in labs were attributed to the recent trial of lithium, and no medication changes were made at that time. Around this time, the patient began complaining of "not feeling good," including congestion and weakness. Temperature remained normal with mild tachycardia.

Repeat labs on day 29 showed improvement in his kidney function (SCr 1.99 mg/dL, BUN 16 mg/dL, eGFR 41 mL/min/1.73m^2) and absence of eosinophilia. His current medications, including clozapine, were continued. On day 35, SCr was again elevated (2.72 mg/dL) and even higher than the previous value. At this time, BUN was 22 mg/dL, and eGFR decreased to 28 mL/min/1.73m^2. His complete blood count again showed eosinophilia (1307 cells/μL).

Over the next month, the patient's kidney function further declined, and he continued to demonstrate eosinophilia and mild tachycardia. A nephrology consult was ordered but, unfortunately, could not be scheduled until the following month. At this point, 8 weeks after beginning clozapine, SCr was nearly 3 times the baseline value (3.22 mg/dL), BUN was elevated but still normal (25 mg/dL), and eGFR continued to decrease to 23 mL/min/1.73m^2. Serum concentrations drawn at this time reflect clozapine of 98 ng/mL and norclozapine of 18 ng/mL on a dose of 62.5 mg/d. Proteinuria was discovered for the first time on day 57.

The clinical pharmacist reviewed the literature for other possible medication causes. Based on his symptoms and the timing of onset, it was agreed that clozapine-induced acute interstitial nephritis was a possibility and that the risks of continuing clozapine without an imminent nephrology consult were too great. Despite robust response to a maximum daily dose of 62.5 mg, clozapine was discontinued only 59 days after initiation. It should be noted that he did not develop a rash, fever, liver abnormalities, or leukocytosis at any point, making the diagnosis of drug reaction with eosinophilia and systemic symptoms unlikely.

Four days following discontinuation of clozapine, the patient's eosinophilia had completely resolved (285 cells/μL), and proteinuria resolved within 3 weeks. Almost 2 years after clozapine discontinuation, he remains eosinophilia and proteinuria free. His kidney function initially worsened to SCr 3.38 mg/dL, BUN 33 mg/dL, and eGFR 22 mL/min/1.73m^2. However, these have slowly recovered although not quite back to baseline: SCr 2.17 mg/dL, BUN 24 mg/dL, eGFR 37 mL/min/1.73m^2. It is likely that the delay in diagnosis and clozapine discontinuation is what led to continued renal insufficiency in this patient. He remains psychotic, continues his skin picking and hoarding behaviors, and is occasionally violent and sexually inappropriate. Current psychiatric medications include loxapine 100 mg PO (by mouth) twice daily, quetiapine 300 mg PO twice daily, fluoxetine 60 mg PO in the morning, diazepam 2 mg PO 3 times daily, benztropine 1.5 mg PO twice daily, and amantadine 100 mg PO every other day.

Literature Review

A PubMed search was performed through October 2018 with search terms including clozapine, acute interstitial nephritis, acute renal failure, acute kidney injury, renal failure, and nephritis. References of articles from the search were also screened for inclusion. Articles are summarized in the Table.

Fourteen cases[2-15] of clozapine-associated renal failure or nephritis were identified, 9 men and 5 women with ages ranging from 24 to 69 years (average 42 years). Doses of clozapine ranged from 25 to 700 mg/d with an average of 218.75 mg/d. Time to symptom onset ranged from less than 1 day to 3 months with an average of 20 days from clozapine initiation. In the cases that reported the following, fever was present in 11/11 cases[2,3,5,6,9-15] (100%), eosinophilia in 6 cases[3,5,11,12,14,15] (of 8; 75%), elevated C-reactive protein in 5/5 cases[2,4,10,13,15] (100%), and proteinuria in 10/10 cases[2,3,5,8,10-15] (100%). Six of the cases[2,4,5,7,9,10] had renal biopsies performed that showed acute interstitial nephritis, and the others[2-4,6,10,11,14,15] were diagnosed by other subjective and objective markers. Clozapine was discontinued in all cases, and

TABLE: Clozapine-associated renal failure reports in the literature

Study	Age, y	Sex	CLZ Dose, mg/d	VPA	Li	Time to Symptom Onset	Fever	Eosinophilia	Elevated CRP	Proteinuria	Biopsy Result
An et al[2] (2013)	38	M	200	Yes	No	14 d	Yes	No	Yes	Yes	Not done
Au et al[3] (2004)	33	M	100	Yes	No	1 wk	Yes	Yes	N/R	Yes	US: glomerular nephritis
Caetano et al[4] (2016)	25	M	300	No	No	20 d	N/R	Yes	Yes	N/R	US: no abnormality
Chan et al[5] (2015)	29	F	700	No	No	7 d	Yes	N/R	N/R	No	Tubulo-interstitial nephritis
Cherry et al[6] (2016)	67	M	200	No	No	19 d	Yes	N/R	N/R	N/R	Not done
Elias et al[7] (1999)	38	F	250	No	Yes	11 d	N/R	N/R	N/R	N/R	Acute interstitial nephritis
Estébanez et al[8] (2002)	69	M	N/R	Yes	No	3 mo	N/R	N/R	N/R	Yes	Acute interstitial nephritis
Fraser et al[9] (2000)	49	M	N/R	No	No	10 d (first trial), 2 d (rechallenge)	Yes	N/R	N/R	N/R	Acute interstitial nephritis
Hunter et al[10] (2009)	57	F	25	Yes	Yes	<1 d	Yes	Yes	Yes	Yes	Not done
Kanofsky et al[11] (2011)	28	M	125	Yes	Yes	7 d	Yes	Yes	N/R	Yes	Not done
Mohan et al[12] (2013)	53	F	200	Yes	No	2 wk (first trial), 60 d (rechallenge)	Yes	Yes	N/R	N/R	Acute interstitial nephritis
Parekh et al[13] (2014)	54	M	100	Yes	No	2 mo	Yes	Yes	Yes	Yes	Tubulo-interstitial nephritis
Siddiqui et al[14] (2008)	26	M	125	Yes	Yes	2 wk	Yes	Yes	N/R	Yes	Not done
Southall et al[15] (2000)	24	F	300	No	No	8 d	Yes	Yes	Yes	Yes	Not done

CLZ = clozapine; CRP = C-reactive protein; F = female; Li = lithium; M = male; N/R = not reported; US = ultrasound; VPA = valproic acid derivatives.

patients were treated with supportive therapy, steroids, antibiotics, and/or hemodialysis. Kidney function returned to baseline in 6 cases[2,4,5,7,9,10] (of 11; 54.55%) and improved but not back to baseline in 5 cases[3,6,12-14] (of 11; 45.45%). One case[15] reported normal SCr throughout, and 2 cases[8,11] did not report kidney function outcome.

It should be noted that 8 cases[2,3,8,10-14] (of 14; 57.14%) were receiving concomitant sodium valproate when symptoms occurred, and only 4 cases[7,10,11,14] (28.57%) were also receiving lithium. It is unclear what connection, if any, concomitant sodium valproate has to clozapine-associated renal insufficiency, but this link should be explored in the future. Advanced age does not appear to be a risk factor for the development of clozapine-associated renal insufficiency as the majority of cases occurred in patients under 60 years of age. Three cases[9,10,12] described clozapine rechallenge, either during the same admission or 4 years later in 1 case. In all 3 of these cases, clozapine-associated renal insufficiency reoccurred, necessitating clozapine discontinuation.

Discussion

Although acute interstitial nephritis is listed in the clozapine package insert, most clinicians are unaware of this potentially severe reaction. Even though it is relatively uncommon, clozapine-associated renal insufficiency can cause significant morbidity in patients who are already low on medication options. All of the literature available on clozapine-associated renal insufficiency is in the form of case reports and case series, making it difficult to determine risk factors, diagnostic criteria, and appropriate management.

Similarities between the case patient and those in the literature[2-15] include the time of onset of symptoms (21 days vs 20 days) and the presence of eosinophilia and proteinuria. The case patient, however, did not display

fever, and his kidney function did not improve back to baseline after discontinuation of clozapine, likely due to the delay in diagnosis. Although the diagnosis was not confirmed with renal biopsy, the timing of symptom onset and improvement correspond to initiation and discontinuation of clozapine. For this patient, the reaction with clozapine was deemed *probable* on the Naranjo Adverse Drug Reaction Probability Scale.[16] Interestingly, the case patient was receiving both divalproex and lithium when clozapine was initiated although the lithium was stopped after only a few days. This case contributes even more to the literature about the potential risk factor of concomitant divalproex and lithium for clozapine-associated renal failure and highlights the need for baseline and regular monitoring of renal function in patients receiving clozapine.

Conclusion

Clozapine-associated renal failure is a rare complication of clozapine treatment that can have significant impact on quality of life. This case contributes to the literature on this important adverse effect and highlights the need for early diagnosis. More research should be conducted into the role of concomitant sodium valproate and/or lithium on the risks for clozapine-associated renal insufficiency.

Acknowledgments

The authors thank Dr Uzelia Hall for her contributions to the manuscript.

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