Clozapine-Valproate Adverse Drug Reactions and the Need for a Clozapine Rechallenge Case File

To the Editor: Nielsen and colleagues[1] recently commented on our work[2,3] regarding clozapine-induced acute renal failure (CIARF). These comments were extremely informative and generate further thought on the issue of clozapine rechallenge. The authors[1] state: "It is highly important that any patient who experienced a serious/potentially life threatening ADR [adverse drug reaction] with clozapine who is later rechallenged is reflected in the literature, so that we can learn more about under which circumstances clozapine rechallenge is or is not safe."(p1695) They note that valproate has been suggested as a relevant risk factor in clozapine-induced myocarditis and nephritis.

In a poster presented at the Institute on Psychiatric Services,[4] our group discussed a patient who developed pancreatitis and acute interstitial nephritis (AIN) within 18 days of the initiation of clozapine treatment. Clozapine was not discontinued because long-prescribed valproate and lithium were respectively believed by the treating physicians to be causative. When these medications were discontinued, both conditions improved.

The case is relevant when considering the circumstances under which clozapine rechallenge can be attempted and illustrates how blame may be assigned to a culprit medication. In this case, valproate may be a relevant risk factor, and discontinuation of valproate due to pancreatitis may enable continuation of clozapine when lithium or other medications are stopped due to AIN. The case is a rare example of a patient experiencing multiorgan failure while taking clozapine.

Case report. A 46-year-old Hispanic man with schizoaffective disorder (*DSM-IV* criteria) was hospitalized for agitation and delusions. His psychiatric medications included divalproex, lithium, and risperidone. Lithium, blood urea nitrogen, and creatinine levels were 0.7 mEq/L, 11 mg/dL, and 0.8 mg/dL, respectively. On day 4, clozapine was initiated and titrated to 150 mg/d. Eight days later, the eosinophil percentage and count increased from 4.5% and 400/mm^3 to 11.6% and 900/mm^3, respectively. Four days later, pancreatitis was diagnosed. Divalproex was considered to be causative and was discontinued. The patient was treated with intravenous (IV) cefoxitin and fluids. His pancreatitis improved, but his serum creatinine level rose to 4.8 mg/dL. Lithium, considered the most probable cause of the creatinine increase, was discontinued. (Our group proposed that brief exposure to IV antibiotics, such as cefoxitin, may exacerbate or precipitate CIARF.[2,5,6]) Renal biopsy revealed AIN. A computed tomography scan revealed bilaterally enlarged kidneys and decreasing pancreatic inflammation. The patient recovered from pancreatitis and AIN and was discharged psychiatrically improved. The patient remained on clozapine 150 mg by mouth daily. His eosinophil percentage fluctuated around 4%.

In 2008 when this case was initially reported, it was not generally recognized that during the first few weeks of a clozapine trial, eosinophilia and fever can be harbingers of clozapine-induced failure of various organs. Usually, eosinophilia and fever are benign and resolve spontaneously. The recommendation is to continue the trial unless organ dysfunction is detected.[1,3,7,8]

Our case suggests a successful clozapine rechallenge may depend on discontinuation of certain coadministered medications prior to rechallenge. A case-control study by Ronaldson et al[9] involving hundreds of patients found rapid dose titration and increasing age increased the risk of myocarditis with clozapine. But concomitant use of valproate increased that risk the most, with an adjusted odds ratio of 2.59 (95% CI, 1.51–4.42; $P = .001$).

Approximately 15 case reports[10] of clozapine-induced pancreatitis have been published. These reports include the case of a patient with pancreatitis who, as in our case, had valproate treatment withdrawn and clozapine treatment continued with no further signs of pancreatitis.[10]

There have been at least 14 prior cases of CIARF published.[2,3,11,12] At the onset of acute renal failure, 8 of the 14 patients were on a clozapine-valproate combination, indicating this may be causally associated with the onset of nephritis.

In 2 of the 14 cases, when patients were rechallenged, CIARF recurred.[3] One patient was on valproate when rechallenged[13]; the second patient's only other psychiatric medication was diazepam.[6]

The small number of cases mentioned here underscores the request of Nielsen and colleagues[1] that any examples of rechallenge in patients with serious clozapine ADR be reflected in the literature. Is there a need for a clozapine rechallenge case file or local registries? A case file or registry would encourage a greater and more accessible flow of information and expedite learning under what circumstances a clozapine rechallenge can be safely conducted.

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Potential conflicts of interest: None.

Funding/support: None.

Previous presentation: The case report was part of a poster presented at the 60th Institute on Psychiatric Services; October 2–5, 2008; Chicago, Illinois.

Informed consent: A valid informed consent was obtained from the patient to publish this case report.

Published online: January 5, 2017.

Prim Care Companion CNS Disord 2017;19(1):16l01968
https://doi.org/10.4088/PCC.16l01968

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