Thrombocytopenia associated with clonidine in a case of clozapine-induced sialorrhea

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Abstract

Clozapine is approved by the US Food and Drug Administration for treatment-resistant schizophrenia and mitigation of suicidality in patients with schizophrenia or schizoaffective disorder. Clozapine requires monitoring of adverse events, such as hypotension, myocarditis, cardiomyopathy, seizures, severe neutropenia, and gastrointestinal hypomotility. Sialorrhea is another adverse event that can be bothersome for patients and result in nonadherence or the development of aspiration pneumonia. Clonidine, an $\alpha_{2A}$ adrenergic receptor agonist, is one medication option that can reduce or eliminate sialorrhea. Clonidine is generally well tolerated but can contribute to hypotension and sedation. One adverse event associated with clonidine not described in the literature is thrombocytopenia. Reported is a case of clonidine-associated thrombocytopenia when used for the treatment of clozapine-induced sialorrhea.

Keywords: clozapine, sialorrhea, thrombocytopenia, drug safety, clonidine

Background

Clozapine is a second-generation antipsychotic that is approved by the US Food and Drug Administration for treatment-resistant schizophrenia and mitigation of suicidality in patients with schizophrenia or schizoaffective disorder. Clozapine requires intensive clinician monitoring to detect and prevent adverse events including, but not limited to, severe hypotension, myocarditis/cardiomyopathy, seizures, severe neutropenia, gastrointestinal hypomotility, metabolic abnormalities, and sialorrhea. The side effect of sialorrhea can be bothersome for patients and may contribute to nonadherence. Clozapine-induced sialorrhea may be transient during an initial titration or persistent, with severity ranging from mild to copious. Clozapine-associated sialorrhea may contribute to the development of aspiration pneumonia and secondary infection–associated clozapine toxicity. These medical complications reinforce the need for vigilant monitoring and appropriate treatment of clozapine-induced sialorrhea.

Clozapine influences the increase of salivation through muscarinic M4 receptor agonism, as well as $\alpha_{2A}$ adrenergic receptor antagonism. These mechanisms provide a rationale for the treatment approach of sialorrhea. Anticholinergic ophthalmic drops (ie, atropine, tropicamide) administered sublingually have minimal systemic absorption, but there is a lack of robust literature supporting their use. If these agents fail or are not suitable, systemically absorbed anticholinergic agents, such as benztrapine or glycopyrrolate, can be considered. Botulinum toxin, metoclopramide, and tricyclic antidepressants are additional agents that have varying degrees of evidence for the management of clozapine-induced
Adrenergic receptor agonists, such as clonidine, have also been reported in case reports to be effective at managing clozapine-induced sialorrhea. Clonidine is generally well tolerated, but it is imperative that clinicians monitor a patient’s blood pressure if clonidine is used concomitantly with clozapine. One side effect of clonidine listed in the prescribing information is thrombocytopenia, but the incidence is not reported. There are also no prior case reports of clonidine-associated thrombocytopenia in the medical literature. We report a case of thrombocytopenia arising during treatment of clozapine-induced sialorrhea with clonidine, followed by complete resolution of thrombocytopenia upon clonidine discontinuation.

Case Report

A 30-year-old male with no past medical history, except a diagnosis of schizophrenia, had a second psychiatric hospitalization for the treatment of worsening delusions and hallucinations. His first hospitalization occurred approximately 1 month prior, and discharge medication was olanzapine 20 mg at bedtime. Also, at that time his platelet count was $156 \times 10^3/\mu L$; reference range is $135 \times 10^3/\mu L$ to $37 \times 10^3/\mu L$ (Figure). Three days prior to the current admission, the patient had self-discontinued olanzapine because of blurry vision. During the hospitalization the patient was trialed on multiple antipsychotics without benefit. Because of persistent psychotic symptoms, clozapine 25 mg at bedtime was initiated on hospital day (HD) 24. A complete blood count (CBC) with differential at that time revealed no derangements, including a platelet count of $156 \times 10^3/\mu L$.

By HD 29, clozapine was titrated to 175 mg at bedtime, at which time the patient started to complain of sialorrhea with nighttime predominance. One drop of ophthalmic atropine 1% sublingually administered at bedtime was initiated but was ineffective after 5 days of use, and the patient was not agreeable to an increase of the drops. The patient reported awakening at least 5 times throughout the night to “spit into a water bottle” and complained of having a wet pillow every morning. Both the bottle of saliva and wet pillow were observed by staff. Clinically, clozapine was increased to target psychotic symptoms, but it was divided as 50 mg in the morning and 150 mg at bedtime in an attempt to minimize sialorrhea. This was not successful to reduce the excessive salivation. Clozapine was further increased to a total daily dose of 250 mg by HD 36 with improvement in psychotic symptoms, although sialorrhea persisted. Clonidine 0.05 mg by mouth twice daily was added on HD 37 to target sialorrhea. On HD 39, the patient reported improvement of sialorrhea, and objectively his pillowcase was found to be dry during morning rounds.

During the first week of clonidine treatment (HD 37-43), the patient’s platelet count decreased from $146 \times 10^3/\mu L$ to $132 \times 10^3/\mu L$. Clozapine had reached a total daily dose of 300 mg by HD 43. On HD 50 the platelet count remained the same, but on HD 52 the platelet count was found to be $117 \times 10^3/\mu L$. All other cell line values were within normal limits. There were no concerns for bleeding, evidence of bruising, or petechiae, but the decision was made to discontinue clonidine given the new thrombocytopenia. Sialorrhea was treated with continued sublingual ophthalmic atropine 1%, 1 drop at night, with the patient...
dependent platelet antibodies is becoming more widely
accepted as needed doses, using on average an
extra 2 to 3 drops per day. Five days later, on HD 58, a
CBC with differential revealed that the platelet count was
within normal limits at $153 \times 10^3/\mu L$. At this time the
patient was also noted to be psychologically ready for
discharge. Delays related to placement issues resulted in
the patient leaving the acute care psychiatric hospital on
HD 84. Discharge medications included clozapine 150 mg
in the morning and 150 mg at bedtime; atropine 1% drops,
1 drop sublingually at nighttime and as needed; melatonin
3 mg at bedtime; and senna/docusate 8.6/50 mg twice
daily as needed for constipation.

**Discussion**

Thrombocytopenia is defined as a platelet count less than
$150 \times 10^3/\mu L$. A platelet count of less than $50 \times 10^3/\mu L$
is associated with spontaneous bruising/purpura and pro-
longed bleeding from wounds. Clinically significant
spontaneous bleeds, such as gastrointestinal bleeding or
intracranial hemorrhage, typically do not occur until
platelets fall below $20 \times 10^3/\mu L$. There are many causes
of thrombocytopenia, including medications. Drug-in-
duced thrombocytopenia can be stratified into non-
immune-mediated and immune-mediated categories.
Non–immune drug-induced thrombocytopenia is associ-
ated with agents that induce bone marrow suppression,
such as myeloablative chemotherapy agents, which
typically affect all hematopoietic stem cell lines. Time to
platelet nadir and time from platelet nadir to recovery are
dependent on the specific agent. A search of the
literature did not find information suggesting clonidine
induces bone marrow suppression. Immune-mediated
thrombocytopenia is associated with platelet destruction
due to the development of platelet-specific antibodies.
This category typically occurs 1 to 2 weeks after drug
initiation or following a single administration if the patient
has previously been exposed to the drug and has
preexisting antibodies. Platelets typically start to recover
1 to 2 days after discontinuation of the offending drug,
with full recovery within 1 week.

The diagnosis of drug-induced thrombocytopenia is
challenging and largely made by excluding other causes
and based on the timing of thrombocytopenia with the
administration of a suspected medication. A possible
limitation in this case when considering the association
between clonidine and thrombocytopenia was that the
empiric discontinuation of clonidine was the sole inter-
vention in this case. No medical consultation or confir-
matory testing was sought, namely because of the lack of
clinical signs and symptoms from the thrombocytopenia
and the temporal relationship between clonidine, throm-
bocytopenia, and platelet recovery. Testing for drug-
dependent platelet antibodies is becoming more widely
available to confirm whether a medication is the culprit.
This was not pursued in the present case, again, given the
resolution of the thrombocytopenia and lack of negative
outcomes associated with the reduction in platelet count.
Another consideration is the possibility of pseudothrom-
bocytopenia. This is an in vitro phenomenon that occurs
from a number of reasons, such as platelet clumping
induced by ethylenediaminetetraacetic acid in the collec-
tion tubes or improper collection technique.21,22 The CBC
analyzer machines at our institution flag samples with the
potential presence of platelet clumps, and in this case
there was no such flag. The identification of potential
platelet clumps would have prompted the need for
manual assessment via a stained peripheral blood smear.

There were no published reports identified in a literature
search associating thrombocytopenia with clonidine, and
this adverse effect is only documented in the prescribing
information with unknown incidence. Drug manufacturers
of clonidine were contacted to gather additional informa-
tion, but they could not provide any additional details
related to thrombocytopenia (Boehringer-ingenheim, Teva,
Mylan, Mayne; oral communication, February 2019). Many
medications, such as carbamazepine, valproic acid and
derivatives, and antipsychotics, have been document-
ed18,19,23,24 as inducing thrombocytopenia in patients
without other risk factors for low platelet count. Clozapine
is also associated with isolated thrombocytopenia in
postmarketing reports and case reports.25,26 In these case
reports, platelet counts only recovered upon clozapine
discontinuation, making clozapine an unlikely culprit in
the case presented above. The only other medications the
patient was administered during the time the platelet
count declined were melatonin and atropine drops,
neither of which has a known association with thrombo-
cytopenia, and they were still continued at the time of
discharge. There were no other medications administered
during the hospitalization that could explain thrombocy-
topenia (eg, heparin for venous thromboembolism pro-
phylaxis, histamine H2-receptor antagonists). Delayed
thrombocytopenia as a result of risperidone, haloperidol,
or olanzapine also is unlikely given the temporal
relationship between platelet count decline following
clonidine initiation and platelet recovery following cloni-
dine discontinuation. Assessment of the case using the
Naranjo probability scale27 indicates objective evidence of
thrombocytopenia, confirmed by CBC testing (+1).
Although there have not been previous conclusive reports
of this event (+0), the thrombocytopenia did appear after
clonidine administration (+2), and platelet count improved
upon clonidine dose lowering and discontinuation (+1, +1).
A lack of formal testing made it unknown if there were
other causes of thrombocytopenia (+0), and serum
clonidine levels were not warranted (+0). There was no
rechallenge (+0), placebo given (+0), or history of
thrombocytopenia occurring prior to this event (+0). In
summary, there was a probable relationship between the initiation of clonidine and the decline in the patient’s platelet count.

Conclusion
Clozapine is associated with a significant number of adverse events, including sialorrhea. Sialorrhea is bothersome to patients and can be treated pharmacologically, but monitoring for adverse events from added medications is crucial. In this case clozapine was used to mitigate sialorrhea but was associated with thrombocytopenia that resolved upon discontinuation. Although this is the first known case report of this adverse event published in the medical literature, clinicians should be aware of the potential for thrombocytopenia in patients treated with clonidine.

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