Author’s response to reviews

Title: Severe intoxication caused by sodium-glucose cotransporter 2 inhibitor overdose: a case report

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Dr. William Spenceley Jones
Assistant Editor
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Subject: Submission of revised paper PHAT-D-19-00267, titled “Severe intoxication caused by sodium-glucose cotransporter 2 inhibitor overdose: a case report.”

Dear Dr. William Spenceley Jones,

Thank you very much for the reviewers’ comments. We have carefully reviewed the comments and have revised the manuscript accordingly.

Our responses are given in a point-by-point manner below. Changes to the manuscript are shown in red. For the readers’ better understanding, we added a label of “time since ingestion” for the horizontal axis in Figure 1.
We hope the revised version is now suitable for publication and look forward to hearing from you.

Sincerely,

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Response to Reviewer 1:

Q1. Page 2, line 38: "Her blood glucose level declined slightly but was in the normal range due to glucose". I am curious to know that why you administrated glucose prophylactically.

A1. Your comment is important. Her blood glucose level was 77 mg/dl, the lower limit of the normal range. However, as shown in Figure 1, her blood glucose level continued to decline 40 hours after drug ingestion. Considering the situation, we prophylactically administered glucose.

We have revised the text as follows (Page 5, lines 87-89).

Her blood glucose level was at the lower end of the normal range, but continued to decline after 40 hours of ingestion, so she was treated with glucose prophylactically.
Q2a. Page 7, line 67-80: Any explanation for bradycardia and hypotension? If this is a slight hypotension (that I believe is not), using norepinephrine is against it.

A2a. Thank you for pointing this out. The patient’s heart rate was 47 beats/min, and blood pressure was 66/26 mmHg (Page 4, line 67-68). This hypotension was thought to be due to ARB and CCB overdose, both of which have been reported as a risk factor for hypotension [8-9].

Her bradycardia was thought to be due to CCB overdose. A normal dose of dihydropyridine calcium channel blocker results in arterial vasodilation and reflex tachycardia, but in high doses, the peripheral selectivity is reduced and it can also affect the myocardium causing arrhythmias, bradycardia and negative inotropy [10]. In particular, azelnidipine has a stronger inhibition of sinus node autoactivity due to the blocking action of L-type calcium channel compared to nifedipine or amlodipine. Therefore, her bradycardia was possibly due azelnidipine overdose.

We added the following sentences in the Discussion (Page 6, line 111-112).

Her bradycardia was probably due to the overdose of azelnidipine, an L-type calcium channel blocker [10].


Q2b. Page 5, lines 90-91: Needs reference

A2b. Thank you for pointing out. We have referenced to the paper in Discussion and Conclusion area (Page 5, line 102-105) that SGLT2 inhibitors are prone to hypoglycemia when combined with other diabetes drugs.

(Page 5, line 102-105)

One of the reasons the patient did not show severe hypoglycemia might be because she did not take other glucose-lowering agents at the same time which have been reported to induce severe hypoglycemia [6].
Response to Reviewer 2:

Q1. We need to clarify about the effect of Azelnidipine which may cause hyperglycemia (opposite effect of) this effect may play a role for decrease the risk of hypoglycemia. Through CA channel blockade L type CA channel in pancreas and insulin resistance at cellular level.

How common this medication causing hypoglycemia. In literature review?

A1.

You have raised an important question. We agree with the possibility that azelnidipine had a role for decreasing the risk for hypoglycemia. As far as we searched, there have been reports of hyperglycemia due to nifedipine overdose, but no reports of azelnidipine overdose. In the drug label of azelnidipine, the risk of hyperglycemia was not reported, and hypoglycemia was reported as unknown. Unfortunately, insulin was not measured in this case.

We have amended the manuscript as follows.

(Page 6, line 116-118)

Another reason for avoiding hypoglycemia might be an overdose of CCB [9]. The increasing blood glucose due to azelnidipine overdose could mask the hypoglycemia due to the SGLT2 inhibitor.

Q2. The author should be mentioned what is the treatment of delusional disorder the patient is taking?

A2. Thank you for your suggestion. She was treated with a number of medications but was not doing well. At the time of overdose, sodium valproate and chlorpromazine hydrochloride were key drugs for her.

We have added the following sentences (Page 3, lines 63-64).
She was treated with sodium valproate and chlorpromazine hydrochloride for her delusional disorder.

Thank you once again for your valuable comments and suggestions. We are hopeful that our supplementary analyses and revised focus helps to improve your opinion of work.