A report of QTc prolongation in a massive multi-drug overdose involved Nortriptyline and Livergol

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Abstract

We report the case of a massive Nortriptyline and Livergol overdose, presenting with the typical Nortriptyline intoxication features, including QT prolongation and rapid response to the treatment, which provides a rationale for the safety profile of Silymarin medications with minimal risks of drug-drug interactions.

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Abstract

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key clinical message

As the interests in the use of herbal medicine like Livergol in the treatment of liver diseases, increases, there is a growing need to ensure its safety. This report highlights the good safety profile of Livergol with no considerable interaction between Nortriptyline and Livergol, associated with complicated Tricyclic-antidepressants overdose treatment.

Keywords : Tricyclic antidepressants, intoxication, nortriptyline, Silymarin, Livergol, QTc prolongation

Introduction

Tricyclic antidepressant (TCA) poisoning, including nortriptyline (NT) and amitriptyline, is among the highly prevalent toxicities. They are second-line drugs next to Selective serotonin reuptake inhibitors (SSRIs) in the management of depression. They carry a higher case fatality, of 7.1% deaths per overdose, with more toxic effects than most other antidepressants [1]. Despite the potentially dangerous toxicity of TCAs, they remained commonly prescribed for various forms of depression, anxiety conditions, and chronic neuropathic pains. Common adverse effects of TCA therapy include blurred vision, dry mouth, tachycardia, orthostatic hypotension, cardiac arrhythmia, sedation, constipation, and urinary retention [2].

Silymarin with the trade name of Livergol® is a Silybum marianum seed derivative with antioxidant properties. Silymarin has been highlighted because of its various biological activities such as immune modulator, hypolipidemic, anti-depressant, antifibrotic, anti-inflammatory, sedative, and antitumor properties. Additionally, it is widely used for its well-known hepatoprotective effect. There are very limited reports on the toxicity of silymarin in human studies, so this substance is accepted as a safe herbal product. The most common adverse effects reported on its use include gastrointestinal symptoms, headaches, and dermatological reactions, but little is known about its potential for drug interaction [3, 4].

Reason for report

Considering cardiovascular toxicity as the major dangerous toxicological concern in nortriptyline poisoning, and its possible drug interaction with Livergol when co-administrated, here we report serial ECG changes and QTc prolongation in a multi-Drug Overdose Involving nortriptyline and Livergol.

Case presentation

A 41-year-old woman was presented to the local emergency department (ED), in Torbat-e Heydariyeh, via Emergency Medical Services with altered mental status, following a suicide attempt with Tricyclic Antidepressant. Her prehospital vital signs included: a temperature of 37 °C, a pulse rate of 86/minute, respiratory rate of 16/minute, and blood pressure of 110/70 mm Hg. The patient was unconscious, drowsy, and assessed with a Glasgow Coma Scale (GCS) of 13 out of 15. Gastric lavage was promptly performed and then she was transferred to the referral center for further evaluation.

She was admitted to the inpatient poisoning care of Emam Reza hospital of Mashhad, the next morning. Upon arrival, the patient was non-vocal and unresponsive to the pain. The GCS was estimated at 9-10/15. vital signs and other physical examinations showed acceptable general condition. Normal breath sounds with no rales or murmur were observed. Her medical history was significant for diabetes, ischemic heart disease, and depression. Medications available to the patient included Nortriptyline, Metformin, Livergol, Gabapentin, and Thiamine supplement. She had taken metformin for treatment of her diabetes for years. Upon questioning, it was claimed that she had taken large but uncertain quantities of Nortriptyline, Livergol, Gabapentin, and Thiamine, about 50 pills in total. Social history was positive for waterpipe tobacco smoking.

Due to the patient history mentioned above, we ran a full blood and urine analysis which was positive for TCAs. An ECG on presentation demonstrated a QTc interval of 481 milliseconds at 10 AM (Figure 1). The patient was treated with a vial of bicarbonate and 10 ccs of potassium chloride, intravenous (I.V). the subsequent ECG, at 4 PM, demonstrated QTc shortening to 463 milliseconds (Figure 2). Blood glucose control was managed according to the insulin therapy protocol. ECG, Arterial blood gases (ABG), and urinary output were regularly checked. During this time, she remained hemodynamically stable, and no other abnormality was noted on the serial ECG. She also received I.V pantoprazole (40 mg), and serum therapy had been ongoing since her early admission. A psychiatry consult was ordered to assess suicidal ideation in the context of TCA overdose.

on the evening of the same day, the patient wished for her discharge against the medical advice. The possible risks of an early self-discharge against the medical advice, including; cardiac arrhythmia and heart arrest were explained to her. Even with this explanation, the patient remained intensified with her decision and immediately started the process and got discharged at 5 PM. But on a further phone call follow-up in the next month, the patient was fine with no complications and reported full remission of all symptoms.

Discussion

We report the case of a multiple drug overdose involving Nortriptyline, Livergol, Gabapentin, and Thiamine supplement, which resulted in a QTc interval prolongation presented on ECG on arrival. According to the 2020 Annual Report of the American Association of Poison Control Centers' National Poison Data System, antidepressants are reported among the top 5 substance classes most frequently involved in toxic exposures, and over the past 10 years, their exposure has increased most rapidly and with more serious outcomes, by

5.84% per year or 1,793 cases per year [5]. As a class, TCAs are categorized in the top 25 classes associated with the greatest fatality [6].

Delayed clinical deterioration or even death following a relative stabilization or improvement, days after the ingestion had been previously documented. A previous case, reports a 61-year-old man presenting after an nortriptyline overdose up to 2500 mg, with QRS widening to 240 milliseconds despite the further narrowing of QRS interval, his course got complicated by repeated episodes of wide complex tachycardia and required continuous sodium bicarbonate treatment until day 14 hospitalization [7]. In another case of a patient with an initial nortriptyline level of 1518 mg/L and episodes of generalized tonic-clonic seizures, sodium bicarbonate infusion was administrated for a total of 5 days [8]. however, in all of these cases, significant initial toxicity was observed. Our patient with large ingestion of Nortriptyline still showed no delayed deterioration and responded very well on a short (12 hours) sodium bicarbonate treatment course. In line with the result of our case, in a report by Pierog and colleagues, despite a large amount of amitriptyline ingested, the patient only received therapy for 48 hours [9].

The recommended therapeutic window of NT is defined between 50 ng/mL and 150 ng/mL. Normally, medications with NT start at a low dose, and then gradually increased to reach the optimal therapeutic level. However, the plasma steady-state concentrations of TCAs in the course of treatment vary interindividual, as the therapeutic or toxic concentrations are mostly determined by NT metabolism and clearance rate. But, in general, plasma levels above 150 ng/mL are associated with the incidence of adverse effects [10]. Given that, conventional dosage regimen can lead to toxic concentration in slow metabolizer individuals, as Lee et al. reported a case presenting with adverse effects such as dizziness, dry mouth, and constipation after 6 days prescription of routine dosage of NT [11]. Drug interactions leading to the decreased metabolism rate can be observed in treatment with two or more CYP enzyme metabolizers, resulting in enzyme competition. Shim et al. reported increased blood levels of TCA in schizophrenic patients under treatment of paroxetine, a potent CYP2D6 inhibitor [12].

Several successful studies have been evaluating silymarin's benefits as an anti-inflammatory, anti-diabetic, anti-Alzheimer, and anticancer agent. Due to the extensive therapeutic roles of Livergol in human studies and its wide use in liver diseases, its safety is very important and should be prescribed with caution, especially when co-administered with drugs that carry a narrow therapeutic window. According to pharmacological studies, silymarin was safe at therapeutic doses in humans, only transient side effects like GI discomfort were reported. Silymarin has shown limited effect on the pharmacokinetics of some drugs in vivo; inhibitory effect on cytochrome P-450 enzymes could affect warfarin metabolism. Though it did not have a major effect on drug metabolism, it is suggested that their combination should be used with caution. In total, Livergol has a good safety profile and is well tolerated even at high doses [3, 13].

One major cause of concern in the use of herbal medicine is that they mainly contain physiochemical constituents that may interact with prescription drugs. Regarding the little information available about herbal product potential for drug interaction and pharmacokinetic alternation, healthcare practitioners usually take caution against co-administration of Livergol and pharmaceutical drugs to avoid any possible clinically significant interactions [14].

Outcome

In our case, a suicidal attempt with massive multi-drug ingestion of Nortriptyline and Livergol, the patient presented with the typical Nortriptyline intoxication presentation, including QT prolongation, and rapid response to the treatment, as discussed above. Despite the large amount of Livergol ingested, no significant GI upset or any symptoms associated with Livergol poisoning were observed, which highlights the good safety profile of the Silymarin products like Livergol. There were also no adverse drug-drug interactions observed in co-admiration of these two drugs.

Conclusion

To the best of our knowledge, a high dose of Livergol can be well-tolerated, and only some transient side

effects like allergic reactions, itching, headache, and GI disturbance are sometimes presented. According to the data of our case, there is also no considerable interaction between Nortriptyline and Silymarin products, associated with complicated TCA overdose or treatment.

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Conflicts of Interest

No conflict of interest or extra-institutional commercial funding exists for any of the authors associated with the manuscript.

I declare that "none" of the authors listed in the manuscript are employed or represented by the agency related to the government of the Islamic Republic of Iran. there are no benefits or connections to the government of the Islamic Republic of Iran.

Informed consent

Written informed consent from the patient was also obtained.

Author contributions

Somayeh Gharibi: Conceptualization, Supervision, writing the original draft and editing

Hanieh Salmani izadi: Data collection, writing the original draft, and writing review and editing

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Figures

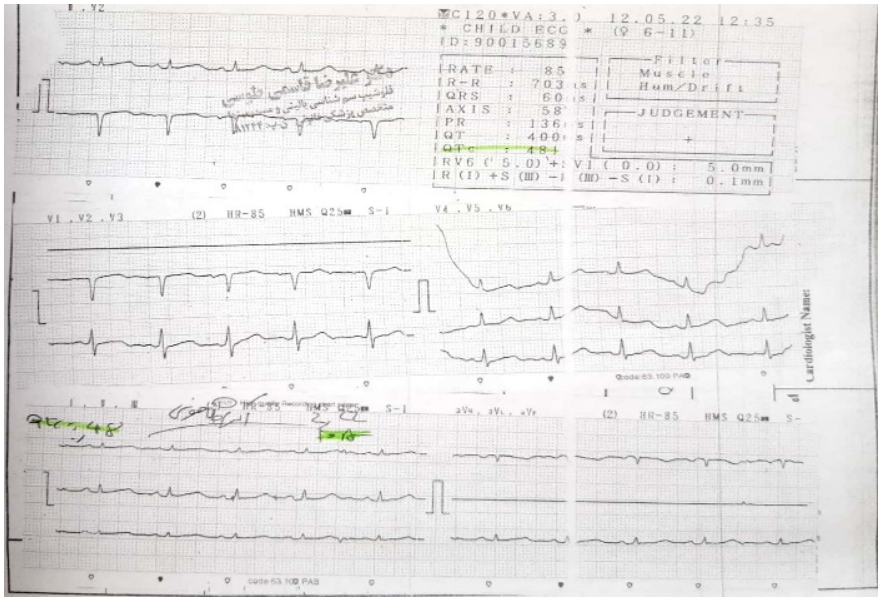


Figure 1: The initial electrocardiogram of a 51-year-old female patient with nortriptyline overdose shows a QTc interval of 481 milliseconds

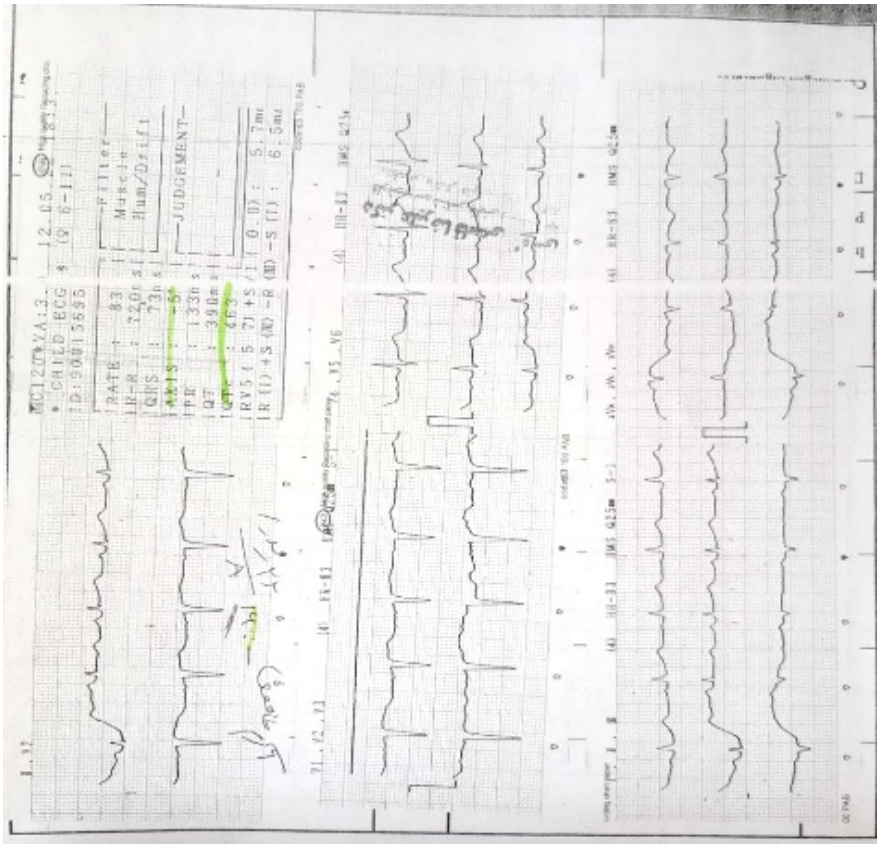
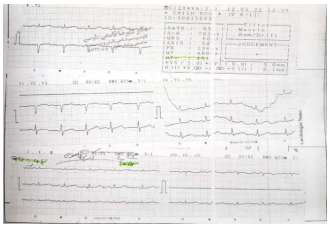


Figure 2: The subsequent electrocardiogram of the same patient after initiation of the therapy, reveals QTc shortening to 463 milliseconds

Figures



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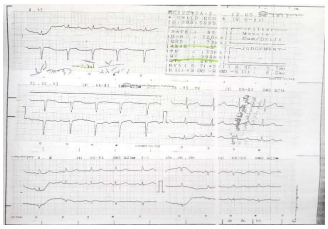

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