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Lurasidone potentiation of toxidrome from drug interaction

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Abstract

Lurasidone, a second generation antipsychotic mediation, is becoming more prevalent in its use due to favourable lower metabolic and cardiac adverse effects. However, long-term efficacy, safety and drug interaction potential of this new drug is not well defined. Here we report a case of 38-year-old woman admitted to intensive care unit with severe refractory hypotension. She was recently initiated on lurasidone therapy as a hypnotic for insomnia management in addition to several regular treatments for her comorbidities including: Quetiapine, paroxetine, lamotrigine, atorvastatin and diazepam. There is limited data on use of intralipid emulsion in severe cardiotoxicity from newer antipsychotics, but when it was used in this case of suspected lurasidone overdose, her profound shock state responded rapidly, with fast weaning off extremely high doses ofepinephrine, norepinephrine and vasopressin.

Keywords

lurasidone; hypotension; polypharmacy overdose; drug interactions; intralipid; intensive

Introduction

Patients with psychiatric disorders, including schizophrenia and bipolar disorder, suffer from multiple medical comorbidities and substance abuse conditions [1]. Polypharmacy that these patients are exposed to places them at an increased risk of drug interactions and adverse events [2]. The use of new antipsychotic agents with lower metabolic disturbance and cardiac adverse effect profile such as lurasidone is preferable; however long-term efficacy, safety and drug interaction potential is not well defined. Additionally, the safety of these agents during deterioration in psychiatric state and exposure secondary to self-harm and overdose is not sufficiently known with only a few reported case studies identified in medical literature [3]. We report a case of 38-year-old woman who potentially overdosed and had multiple drug-drug interactions while on treatment with second generation antipsychotics, anti-depressants and antiepileptic agents resulting in profound circulatory collapse. Due to the profound shocked state, intralipid emulsion therapy was used, which resulted in a dramatic response and rapid recovery from the near-death situation.

Case Report

Thirty-eight year old female with a known history of depression and previous self-harm was brought to our hospital's Emergency Department (ED) at 0130 hours by ambulance in an altered

conscious state and profound hypotension. She suffered from severe depression with features of borderline personality disorder as evidenced by multiple laceration scars of varying ages on her forearms. Her regular medications included: quetiapine 50mg daily, lurasidone 40mg per day, paroxetine 40mg once a day, lamotrigine 200mg a day, atorvastatin 20mg per day for hypercholesterolemia, cholecalciferol 25µg per day, folic acid 0.5mg per day, and magnesium aspartate 1000mg at night for restless leg syndrome along with diazepam 5mg twice a day for management of anxiety and zopiclone 15mg at night for insomnia, as and when required.0 She claimed that lurasidone was commenced for insomnolence after failing other pharmacological therapies with quetiapine, mirtazapine and melatonin for sleep without any benefit. These drugs were found in her possession on hospital admission.

She was found unresponsive in the garage by her mother around midnight. She had apparently gone out to smoke an hour before being found after complaining of feeling exhausted. When the paramedics arrived at the scene, they observed the patient to have a Glasgow Coma Scale (GCS) of 3/15, tachycardia (160 beats per minute) and hypotension (70/45 mmHg). As the patient's blood pressure remained refractory to IV fluids epinephrine (adrenaline) infusion was commenced, which was soon titrated up to 100 µg/minute (1.33 µg/kg/minute) to maintain the haemodynamic status, with 2mg of epinephrine (adrenaline) given during transport to the hospital. In the ED, she remained hypotensive (systolic blood pressure of 60-70 mmHg) despite receiving 6.5 litres of crystalloid volume resuscitation and being on adrenaline infusion at 100 µg/minute (1.33 µg/kg/minute). Noradrenaline (norepinephrine) was commenced following a central line insertion along with ongoing adrenaline infusion. She was intubated safely for airway protection. As her haemodynamic situation was dire with escalating noradrenaline dose (rapidly to 100 µg/minute (1.33 µg/kg/minute), hydrocortisone 250mg was administered along with empirical antibiotics, which included vancomycin 2 grams and piperacillin/tazobactam 4.5 grams. Vasopressin infusion was also added at 0.04 Units/hour due to inability to maintain a target mean arterial pressure of 65 mmHg. Bedside transthoracic echocardiogram (TTE) revealed global cardiac dysfunction suggestive of more systemic pathology. Electrocardiogram (ECG) showed sinus tachycardia with rate-related wide spread ST depression in chest leads. QRS and QTc intervals were not prolonged. The exact aetiology was unclear; however, the working diagnosis was polypharmacy overdose of psychotropic drugs.

The differential diagnosis was toxic shock syndrome from tampon use, or cardiomyopathy related to long-term use of psychotropic medications or an infection. The profound cardiogenic shock state that the patient was in, which was minimally responsive to very high doses of inotropic and vasopressor supports along with a polypharmacy overdose concerns prompted the treating team to administer a single dose of Intralipid Emulsion (ILE) 112ml (1.5ml/kg). While paracetamol (acetaminophen) levels were awaited, she was started on N-acetyl cysteine infusion as per protocol (150mg/kg over 1-hour, 50mg/kg over 4-hours and 100mg/kg over 16-hours). The patient's haemodynamic state briefly improved that facilitated her safe transfer to intensive care unit (ICU).

On admission to ICU, the haemodynamic supports continued to increase. Continuous renal replacement therapy (CRRT) was urgently commenced for worsening severe metabolic acidosis (pH: 6.98, Lactate: 8.7 mmol/L). Her case was discussed with ICU specialists in quaternary centres for extracorporeal membrane oxygenation (ECMO) suitability. The ECMO team advised that the patient

would be considered if the clinical condition did not improve over the next 24 hours. A Toxicologist was consulted, who opined that further doses of Intralipid infusion may not be beneficial and advised weaning off adrenaline due to competitive binding by the atypical antipsychotic with activation of ß-2 receptors by adrenaline leading to additional hypotension.

The treating team administered ILE infusion at 0.25ml/kg/minute for 2 hours despite the Toxicologist's advice, giving in total 1 litre of ILE. Patient's clinical condition improved dramatically over the next 4 hours of ICU admission (11 hours after ED presentation). Epinephrine (adrenaline) was rapidly weaned off following the commencement of ILE infusion, with the rate coming down from 100 µg/minute (1.33 µg/kg/minute) to being complete off within 1 hour. Norepinephrine noradrenaline) infusion rate was also weaned down from µg/minute (1.33 µg/kg/minute) to 50 µg/minute (0.66 µg/kg/minute), by the end of ILE infusion, with further large rate reduction to 4 µg/minute (0.05 µg/kg/minute) within 5 hours with vasopressin reduction to 0.02 Units/hour within the same period. The patient was completely weaned off of all pharmacological vasopressor support within 20 hours of ICU admission. Repeat bedside TTE showed complete recovery of her myocardial function. Serial ECGs demonstrated normalisation of ST depression. The CRRT was ceased within 24 hours once her metabolic state normalised. The patient developed mucopurulent sputum with a chest X-ray confirming right lower lobe opacification, which delayed extubation. She was successfully extubated after 56-hours of ICU stay without any neurological sequelae. Antibiotics were deescalated to amoxicillin and clavulanic acid.

She was discharged from ICU to a medical unit on day-3 for further care following a thorough assessment by a psychiatrist who recommenced recommencing paroxetine at 20mg per day. During her admission, she denied taking the overdose. She was discharged home on the fourth day of hospitalisation with oral antibiotics and paroxetine, and a follow-up appointment organised with her private psychiatrist.

Discussion

Lurasidone, benzothiazol derivative, is a novel antipsychotic mediation that has high affinity for dopamine-2, 5-hydroxytryptamine 2A (5-HT2A) and 5-hydroxytryptamine 7 (5-HT7) receptors, moderate antagonist activity at α-2A and α-2C adrenergic receptors and partial agonist activity at 5-HT1A receptors [3], but has little affinity for histamine H-1 receptors or M-1 muscarinic receptors. It has approved indications by the Food and Drug Administration for schizophrenia and depression in bipolar disorder and by Therapeutic Goods Administration for treatment of schizophrenia [4]. Due to its minimal affinity for α-2 receptors it is less likely to cause major cardiac effects and metabolic disturbances. To our knowledge, there is limited literature available on intentional overdose of lurasidone or its drug interactions [3,4].

Lurasidone's pharmacokinetics need to be carefully considered in management of overdoses, to limit toxicity and to expedite recovery. Lurasidone is 99.8% protein-bound, with primarily hepatic elimination via cytochrome CYP3A4 enzymatic pathway and a reported half-life of 12-18 hours, with only 0.1% excreted unchanged in the urine [3,7]. Lurasidone produces both active and inactive metabolites [5-8]. Thus, there is potential for drug-drug interactions between lurasidone and drugs that are metabolised by CYP3A4, as well as inducers and inhibitors of CYP3A4 [9,10] increasing the metabolites of lurasidone or potentiating lurasidone itself. Pharmacokinetics of lurasidone are also influenced by

energy-dependent efflux transporter P-glycoprotein (P-gp) [11], and there is significant overlap between substrates of P-gp and those of the CYP3A4 including common antidepressants such as amitriptyline and citalopram [12].

Psychiatric patients with severe chronic depression and other medical conditions are more likely to have access to drugs with interacting pharmacokinetics, which may lead to emergence of less common and rare adverse events. The cardiovascular adverse effects of lurasidone such as tachycardia and hypotension (α-2 receptor blockade) [6,13], were the predominant features in our patient, which are considered to be common and rare respectively. Although blood dyscrasias, akathisia, Parkinsonism, nausea and somnolence are other possible adverse effects [6,13], our patient did not experience these during her presentation to ED or ICU. However, suicidal behaviour has been reported in the product information as a rare adverse reaction[6].

Lurasidone is the only antipsychotic drugs that does not prolong QTc duration [14], which was evident in our patient. A high index of suspicion should hence be maintained as these newer agents lack constellation of ECG features that are characteristic for severe toxicity such as QRS widening and prolongation of Qtc.

The circumstances of the toxidrome was unclear. Although drug levels of lurasidone could not be measured, from the history of overdose and concomitant drug-drug interaction we can hypothesize that lurasidone could be the potential causative agent for haemodynamic and neurological compromise of the patient. There are various mechanisms to explain this presentation, assuming that our patient did not consume an intentional overdose.

Quetiapine and zopiclone are metabolised by CYP3A4, while paroxetine is a weak inhibitor of CYP3A4 [14,15]. Our patient was on a combination of quetiapine, zopiclone and paroxetine, all of which may have enhanced the lurasidone metabolites, increasing its toxic profile [14-16]. It is recommended that drugs that are strong CYP3A4 inhibitors or inducers should not be co- administered with lurasidone, however, it may sufficient for toxicity to emerge from polypharmacy interactions [3]. While the patient presented in this report was prescribed only 40mg of lurasidone daily, and even though the recommendations suggest that lurasidone dose should not exceed 80 mg/day when co-administered with a moderate CYP3A4 inhibitor [5], we suspect that lurasidone toxicity can occur at lower doses and high index of suspicion should be maintained.

Diazepam is a highly protein-bound drug that can potentially increase the free drug concentration of lurasidone by displacing or competing for protein binding, further contributing to direct lurasidone toxicity, as well as increasing its availability for metabolism and a rise in active metabolites [15]. Collateral history suggested of alcohol / wine consumption (grape juice) that can further enhance lurasidone activity [16]. To our knowledge, there are no documented case studies on the use of Intralipid emulsion (ILE) therapy in lurasidone toxicity. In our patient we noticed promising improvement in haemodynamic status immediately after ILE administration. ILE therapy has been extensively studied in local anaesthetic agents-related systemic toxicity. It has been shown to be a promising antidote in cardiac arrest due to lipophilic drug poisoning or overdoes (β-blockers, calcium channel blocker overdoses, tricyclic antidepressants and other psychotropic drugs) [17-19] by exerting a “lipid sink" effect and thus reducing the concentration of active drug / metabolite in the target tissue and decreasing toxicity. Given

the response observed in the case presented in this report, ILE could have had the same effect on lurasidone.

Conclusions

Lurasidone toxicity can occur at lower therapeutic doses in patients due to drug-drug interactions following co-administration with other treatments the affect the CYP3A4 enzyme metabolic pathway. A high index of suspicion should hence be maintained as these newer agents lack constellation of ECG features that are characteristic for severe toxicity such as QRS widening, prolongation of QTc and obtaining drug levels is technically challenging. Intralipid emulsion (ILE) could be a life-saving and cost-effective early treatment modality in patients who experience profound systemic cardiovascular compromise refractory to high dose vasopressors and inotropes.

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