Olanzapine overdose in an elderly man in south-east Nigeria.

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Abstract

Background: Olanzapine is a commonly used, relatively safe antipsychotics but in overdose, its adverse effect may be remarkable, especially in elderly.

Aim: To express the clinical features and outcome of Olanzapine overdose in elderly.

Case: A 65year old, known psychiatry patient who has been on Olanzapine tablet, presented with rigidity, tremors, difficulty in speech, body weakness more severe on the legs, dizziness and repeated falls. There was no fever, head injury, impaired consciousness, synchronous jerky movement, urinary or biting of the tongue. He has not had stroke, diabetes or hypertension before. He was in control of his thoughts; no strange experiences; does not smoke cigarette or cannabis, though drinks alcohol occasionally. Mental state, physical examinations and investigations apart from brain atrophy in brain imaging revealed no further abnormality. Two days on admission, he was mistakenly given 100mg of Olanzapine tablet, 30 minutes later, he slipped into unconsciousness with tachycardia, tachypnoea, laboured breathing, hyperpyrexia and hypotension. The patient was resuscitated with oxygen, fluids and tepid sponging. He regained awareness, and was discharged home on Risperidone on the 13th day of his admission.

Conclusion: The elderly may be considered more sensitive to Olanzapine toxicity.

Introduction

Olanzapine is one of the atypical antipsychotics which belong to the thienobenzodiazepine group. Due to its safety and efficacy, Olanzapine is increasingly used for the treatment of psychiatric disorders (Fulton et al, 1997; Beasley et al 1997). The antipsychotic property has been attributed to its antagonism to dopaminergic D2 and seretoninergic 5-HT2a receptors, however, Olanzapine interaction with other receptors like dopaminergic D1, D4; seretoninergic 5-HT2c; histaminergic H1; cholinergic M1-5; α1 adrenergic receptors may be responsible for the barrage of clinical features observed during toxicity (Majunder et al 2009). Even though the usual dose range of Olanzapine is 5-15 mg/day, there are no standard reference values of expected concentration after giving this therapeutic dose. The steady-state blood (plasma) concentration of Olanzapine in clinical setting is rarely above 150ng/ml (Zyprexa 1996), however, the potential for toxicity has been suggested at concentrations as low as 100ng/ml (Robertson et al 2000). The rate of metabolism of Olanzapine varies markedly (up to 20 fold) among different individuals. In large overdoses, non-linear pharmacokinetics occurs leading to tremendous increases in blood concentration due to extensive first pass metabolism of about 40% (Bosch et al, 2000). Olanzapine is extensively metabolized in the liver (Prior et al, 1999), and impairment in enzyme mediated metabolism may result in varied blood concentrations. Hiemke et al, 2000 reported 2 fold and 3 fold increases of Olanzapine blood concentration when 5mg/d and 20mg/d respectively were given in combination with Fluvoxamine suggesting competitive inhibition. The symptoms in Olanzapine toxicity is a reflection of its pharmacological properties and may include: somnolence, mydriasis, blurred vision, respiratory depression, hypotension and extrapyramidal and anticholinergic effects (Dougherty et al, 1997; Dobrusin et al, 1999; Schwartz et al 1997; Cohen et al, 1999). A case of Olanzapine toxicity of 800mg with corresponding serum concentration of 991ng/mL manifested clinical symptoms and signs like:

central nervous system depression, tachycardia, hyperpyrexia, leukocytosis, elevated creatine phosphokinase levels and paradoxical miosis mimicking opioid or α_2-agonist intoxication (Cohen et al, 1999; Bosch et al, 2000; Powell et al, 1997; O`Malley et al, 1999; O`Malley et al, 1998; Fogel et al, 1998). Altered mental status following Olanzapine overdose was successfully treated with physostigmine as reported by Witzberg et al, 2006. Rapid recovery with the use of activated charcoal was reported by Gardner et al, 1999 in a 29 year old woman who took 1110mg of olanzapine and developed tachypneoa, tachycardia, unstable blood pressure and hypoxaemia. Early administration of activated charcoal may reduce the oral bioavailability of olanzapine by 50-60% (Gardner et al 1999). There is no definitive antidote for Olanzapine till date, and supportive treatment remains the main stay of therapy (Niraji et al, 2017). Although the exact pathophysiology is not known, it has been suggested that the most likely cause of death in Olanzapine overdose involves cardiotoxicity at the cellular membrane level (Gerber et al, 2000), however, there are no data supporting direct cardiac toxicity of Olanzapine. A data mining study of the World Health Organization (WHO) database of adverse reactions identified a strong signal for a link between clozapine, cardiomyopathy and myocarditis (Coulter et al, 2001) and for antipsychotics as a group; but in fact, there were fewer reports for olanzapine than for haloperidol or risperidone. An analysis of 85 fatal intoxications reported that pimozide and Olanzapine were less likely to be associated with death in overdose than prothipendyl and chlorprothixene (Schreinzer et al, 2001).

Not many studies have reported clinical presentations of Olanzapine toxicity in the elderly in our environment, so this report serves to add to the body of existing knowledge.

Case

A 65 year old man, who is a known psychiatric patient being managed for psychosis and has been regularly on Olanzapine and Benzhexol tablets, presented to Enugu State University Teaching Hospital (ESUTH) with complaints of rigidity, mild tremors on both hands, difficulty in speech, extreme general body weakness more severe on the legs, dizziness and repeated falls on the ground. There was no associated history of fever, head injury, impaired consciousness, synchronous jerky movement of the limbs, loss of urinary or faecal continence, upward rolling of eyeballs, nor biting of the tongue. He has not had stroke in the past and he is not a known diabetic or hypertensive patient. He was in full control of his thoughts, no strange experiences like hearing strange voice(s) or seeing strange things others don`t hear or see in clear consciousness. He does not smoke cigarette or cannabis, though drinks alcohol occasionally. Mental state examination revealed a calm, kempt, cooperative patient with good eye to eye contact and involuntary movement of the upper limbs. The speech was not spontaneous but, coherent and relevant. There was neither formal thought disorder nor perceptual abnormalities. The physical examination showed a conscious and alert elderly man, not pale, not dehydrated, not cyanosed, anicteric, no lymphadenopathy, no bilateral pedal oedema. There was no cranial nerve deficit, but had cogwheel rigidity across the joints, power of 4/5 on both lower limbs and 5/5 on upper limbs. Global normotonia, normoreflexia and shuffling gait were also noted. All the other system examinations were essentially normal. Laboratory investigations like: full blood count (FBC); serum urea, electrolyte and creatinine (SUECr); liver function test (LFT) and fasting blood glucose (FBG) were all normal. Brain Magnetic Resonant Imaging (MRI) only reported mild brain atrophy and Electroencephalogram also showed no abnormality. He was subsequently admitted into the ward and was managed as a case of Psychosis in remission with

extrapyramidal side effect (EPS) due to Olanzapine. The plan was to gradually tail off Olanzapine and introduce another atypical antipsychotic medication and control the EPS. However, 2 days of his admission a Nurse who mistakenly did not observe cancelled prescription administered 100mg of tablet Olanzapine to the patient. About 30 minutes later, he could not respond to call and painful stimuli and gradually went into deep coma with associated tachycardia, tachypnoea and laboured breathing, high grade fever and hypotension. The patient was resuscitated with intranasal oxygen, intravascular fluid and tepid sponging. He regained consciousness but remained drowsy till about 12 hours after ingestion of Olanzapine. Electrocardiogram, repeat (LFT) and SUECr results showed no abnormality. Olanzapine was gradually withdrawn from his drugs and introduced low dose Risperidone and Benzhexol. He was discharged home on the 13th day of his admission.

Discussion

With relatively smaller quantity (100mg) of Olanzapine, this patient developed laboured breathing, hypotension, coma, hyperpyrexia which are similar features seen at a much higher overdose of 800mg, 1110mg as has been reported in the literature. This is probably suggesting that the elderly may experience much more morbidity and mortality compared to younger adult in Olanzapine toxicity. Many scholars have reported Olanzapine as a relatively safe antipsychotic in overdose, which may have contributed to the survival of this patient. A detailed review of relative safety of atypical antipsychotics has been reported (Burns et al, 2001). A study of elderly patients by Nasrallah et al, 2001, demonstrated lower mortality rate of atypical antipsychotics toxicity (4.8%) compared with haloperidol of 21.4% over a 2 year period.

Furthermore, a review of 574 inquiries from UK National Poison Information Service over a 9 month period, showed no fatalities following overdoses of atypical antipsychotics (Capel et al, 2000). The researchers opined that olanzapine and risperidone were safer in overdose than clozapine and sulpiride. In addition, the clinical outcome of treated overdoses in hospital settings was better than that of individuals who did not receive active interventions (Capel et al, 2000). In other words, the intranasal oxygen and intravenous fluid instituted immediately after the ingestion of the drug may have contributed to the favourable outcome of this patient in spite of the fact that he has been on olanzapine and had even developed extrapyramidal side effect due to olanzapine before he had the overdose.

Pierre et al, 2003 in review study of Olanzapine toxicity suggested an adverse outcome for patients who has pre-existing undetected physical illness like cardiovascular disease involved in overdose of multiple medications and does not receive any intervention. Other factors which may have contributed to good outcome of this patient may include the fact that he was on Olanzapine monotherapy which eliminated the occurrence of drug-drug interactions that may have heightened the blood level of Olanzapine. Co-administration of Olanzapine and Fluvoxamine led to many fold rises in plasma Olanzapine concentrations (Ereshfsky 1996). Apparently, the patient was not diabetic, hypertensive nor have any other comorbid conditions which may have complicated the Olanzapine overdose if undiagnosed or untreated.

Conclusion

Adverse effects of Olanzapine overdose may be worse in the elderly. In absence of complex polypharmacy of psychotropic drugs, undiagnosed, untreated medical illness, Olanzapine may be relatively safe in overdose even though it has been associated with toxicity in certain cases.

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