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Acute quetiapine overdose is associated with risk of ectopic atrial rhythm

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ABSTRACT

Quetiapine overdose is commonly associated with coma, respiratory depression, hypotension, tachycardia, and QTc interval prolongation on the electrocardiogram. Although the arrhythmogenic effect of antipsychotics on ventricular arrhythmia has been established, their role in atrial arrhythmias is still not quite understood, specifically the ones caused by an ectopic atrial rhythm (EAR). We aim to present a case and review on the association between quetiapine and EAR. Data were obtained from clinical records and bibliographic research on PubMed. We present the case of a 57-year-old woman brought to the emergency room after a quetiapine overdose with a newly diagnosed EAR that reverted hours later. This association may be due to quetiapine's increased risk of cardiac muscarinic receptors blockade that can lead to conduction abnormalities. Because of the possibility of degeneration to other more serious rhythm alterations, pacemaker implementation and increased mortality, there is a need for greater awareness of this correlation.

Keywords. *"Quetiapine", "quetiapine overdose", "ectopic atrial rhythm".*

RESUMEN

La sobredosis de quetiapina se asocia comúnmente con coma, depresión respiratoria, hipotensión, taquicardia y prolongación del intervalo QTc en el electrocardiograma. Aunque se ha establecido el efecto arritmogénico de los antipsicóticos sobre la arritmia ventricular, aún no se conoce bien su papel en las arritmias auriculares, específicamente las causadas por un ritmo auricular ectópico (RAE). Nuestro objetivo es presentar un caso y revisión sobre la asociación entre quetiapina y RAE. Los datos se obtuvieron de las historias clínicas y de la búsqueda bibliográfica en PubMed. Presentamos el caso de una mujer de 57 años que acudió a urgencias tras una sobredosis de quetiapina con una RAE de nuevo diagnóstico que revirtió horas después. Esta asociación puede deberse al mayor riesgo de quetiapina de bloqueo de los receptores muscarínicos cardíacos que puede provocar anomalías en la conducción. Debido a la posibilidad de degeneración a otras alteraciones del ritmo más graves, la implantación de marcapasos y el aumento de la mortalidad, existe la necesidad de una mayor conciencia de esta correlación.

Palabras clave. "*Quetiapina*"; "*sobredosis de quetiapina"; "ritmo auricular ectópico".*

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BACKGROUND

Atypical antipsychotic agents, such as quetiapine, also known as second-generation antipsychotics, are well known for their risk of QT interval prolongation and sudden cardiac death.[1] According to a study performed by Pfizer (Harrigan *et al.*, 2004), 750mg/day of quetiapine was found to increase the mean QTc (corrected QT interval) by 6ms.[2] This particular class is implicated in a significant proportion of deliberate self-poisoning cases in developed countries.[3] As reported by Campleman *et al.*, quetiapine overdose is associated with severe QT prolongation (96 out of 471 reported cases, with a mean difference in QTc between drug exposure and rest of cohort of +14.1ms).[4]

Quetiapine has a formal indication in the treatment of schizophrenia, acute manic episodes, and adjunctive treatment for major depressive disorder. It also has clinical efficacy in the treatment of unipolar depression, generalized anxiety disorder, other psychotic disorders, behavioural changes in Parkinson's disease, insomnia, chronic post-traumatic stress disorder and impulse-control disorder. It can also be used as adjunctive treatment in other conditions such as obsessive-compulsive disorder and borderline personality disorder.[5] Despite the multiple indications, dosages should not exceed 800mg daily.[6] It has a short half-life of 6-7 hours, is rapidly absorbed, and reaches peak concentrations between 1-2 hours. Its major route of elimination is through hepatic metabolism by CYP3A4, followed by excretion of its metabolites in the urine and feces. It works as a serotonin 5HT2A (5-HT2C, 5-HT7), dopamine D2, muscarinic M1 antagonist, 5HT1-A partial agonist and blocks noradrenaline reuptake.[7,8] In comparison to other atypical antipsychotics, quetiapine is less prompt to cause extrapyramidal features.[9]

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Premature supraventricular beats are premature complexes of supraventricular origin that arise above His bundle division and particularly from the atria (premature atrial beats) or atrioventricular (AV) junction (premature junctional beats). Premature atrial beats (PAB) in which the focus is near the AV junction can present an inverted P wave in the inferior leads (II, III and aVF), similar to the ones present in premature junctional beats. To help differentiate these two entities, a PR interval usually ≥ 120ms is indicative of a premature AV junctional complex.[10] PAB is unlikely to result in a prolonged QT or any ventricular arrhythmia, like Torsades de Pointes, since they do not directly influence ventricular repolarization.

The toxicity of quetiapine is variable, and it may be difficult to predict the severity of the poisoning.[11,12] The clinical features of quetiapine poisoning are well-characterized, including early onset sedation, coma, respiratory depression, anticholinergic symptoms, sinus tachycardia, prolonged QT and hypotension. Doses above 3g are associated with coma, however, studies report that the severity of the overdose does not have a direct correlation with a high serum concentration nor with the ingested dose.[13,14,15] We couldn't find literature associating quetiapine poisoning with an ectopic atrial rhythm (EAR).

Our aim with this case is to review the association between quetiapine and EAR.

CASE PRESENTATION

A 57-year-old, female, divorced, with two kids. Currently on unpaid leave after her mother's extended stay in the intensive care unit, for whom she is the main caregiver. Personal history of arterial hypertension. She had a previous medical history of Persistent Depressive Disorder. No relevant family history. Medicated with ethyl loflazepate 2mg daily and trazodone 150mg extended-release daily.

She was brought to the emergency room 30 minutes after being discovered by her mother unconscious and with empty pill bottles surrounding her. At admission her vital signs were stable, and her aspirated gastric content evidenced the intake of multiple pills. At first, she couldn't provide any history due to impaired cognition. Organicity screening was carried out with laboratory studies (blood count, renal function, ionogram, hepatic and thyroid function), as well as chest x-ray without alterations.

Her ECG (electrocardiogram) at admission was compatible with an EAR with a prominent negative P wave recorded in leads II, III and aVF (**Figure 1**). It also showed a regular sinus rhythm of 80 beats per minute (bpm), a QTc of 413ms (calculated by the Bazett formula) and no acute ischemic changes or ST-segment deviations. According to her medical file, previous routine ECG, performed 7 months before, didn't present any alteration.

Upon posterior clinical examination by the on-call psychiatrist, the patient was awake, orientated in person, partially orientated in space and time, with evident depressive mood, with complaints of anhedonia, adynamia, intermediate and final insomnia, significant weight loss (4kg in one month), feelings of worthlessness, psychomotor retardation, and presented a structured suicidal ideation. Concerning her depressive mood, which first started 4 months ago, the patient related it to the troubled relationship with her mother ("*she doesn't approve of my relationship with my new partner*" (...) "*she is always controlling my schedules, making sure I'm always by her side, at all times.*" (...) "*I can't even go to church.*") and a recent car crash her 26-year-old son was involved in, two weeks before admission. The son had a fracture of the spine, wrist and finger, and is awaiting surgery. Regarding the suicide attempt, the patient recollects taking a complete bottle of her mother's quetiapine 50mg pills ("*I took all 60, I couldn't take it anymore.*"), ie 3g (total dosage). The ECG was repeated, 16 hours after the first tracing, this time revealing a normal sinus rhythm of 83bpm, a prolonged QTc of 470ms and no acute ischemic changes or ST-segment deviations (**Figure 2**). The QTc interval normalized spontaneously and within 24 hours after the voluntary drug ingestion episode the patient was voluntarily admitted to the Psychiatry Unit for clinical stabilization with the indication of the on-call Cardiologist to repeat the ECG at the time of discharge. She was hospitalized with the diagnostic of Unipolar Major Depression with structured suicidal ideation. Pharmacological treatment consisted of sertraline 50mg/day that was titrated up to 100mg/day and lorazepam 1mg/day, allied with cognitive-behavioural psychotherapy. The patient was discharged after 19 days, with the remission of the depressive symptoms and dissolution of the prior suicidal ideation. A third ECG was repeated, as recommended, revealing, again, a normal sinus rhythm with no sign of arrhythmias or conduction abnormalities. She was also referred to psychiatric outpatient treatment.

OUTCOME AND FOLLOW-UP

The patient was observed in two appointments after discharge, presenting complete remission of the depressive symptoms and denial of suicidal ideation.

Despite not being referred to cardiology outpatient treatment, the patient did two other ECGs that revealed a normal sinus rhythm with no conduction abnormalities or arrhythmias.

DISCUSSION

The first ECG, performed 30 minutes after the ingestion of quetiapine, is compatible with a premature atrial beat caused by an ectopic foci, hence EAR, near the AV junction, more particularly at the bottom of the atria due to the negative P wave. It is also noticeable that the ectopic depolarization was successfully conducted to the ventricles since a QRS complex is always present, maintaining AV synchrony.

Despite the absence of literature, theoretically, increase cardiac muscarinic blockage produced by quetiapine can lead to conduction abnormalities, which include EAR. The parasympathetic nervous system exerts its cardiac action via muscarinic M2 receptors and, by its blockage, a vagal withdraw would precipitate an ectopic stimuli leading to an EAR. Cardiac muscarinic blockage also causes conduction abnormalities as shown by Hong et al.[16] Patients with EAR also appear to have a high risk of mortality and pacemaker implantation, which was associated with autonomic imbalance, as shown by Huang et al.[17]

This case also demonstrates the importance of ECG monitoring post-ingestion of quetiapine in high dosages due to the possible delayed effect of QT prolongation that only appeared in the second tracing, 17 hours after the suicide attempt.[18]

In conclusion, although there aren't described cases, quetiapine, theoretically, can originate an EAR by the cardiac muscarinic blockage. It still needs to be settled if this association is possible with the pre-established/recommended dosages indicated for the multiple psychiatric disorders or if a minimum dosage is required to cause this cardiac abnormality. Due to the high variability of quetiapine overdose, clinicians must be aware of the possible adverse effects and acknowledge the possible correlation between quetiapine, independently of the dosage, and the appearance of arrhythmias, particularly EAR.

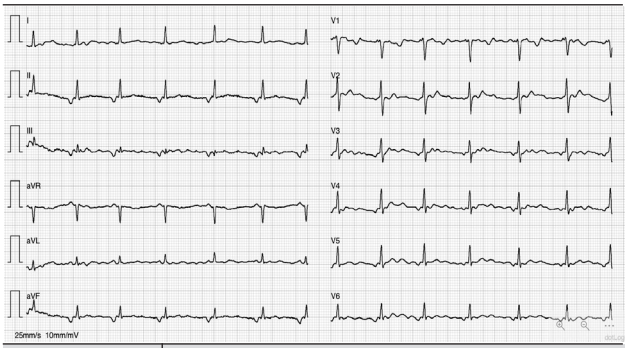

Figure 1 | Electrocardiogram at admission.

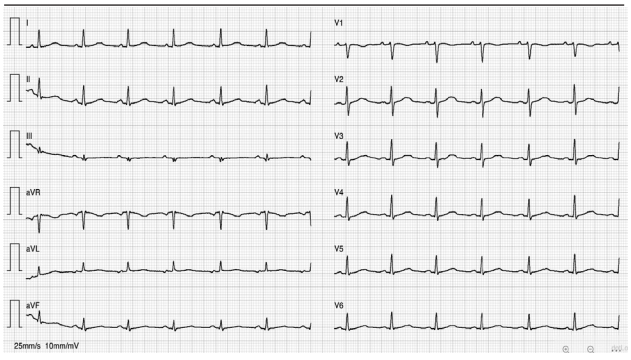

Figura 2 | Electrocardiogram 16 hours after admission.

ETHICAL RESPONSIBILITIES

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