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Ziprasidone overdose: cardiac safety

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Ziprasidone is a neuroleptic drug recently sold in Spain. According to its profile of receptors it is considered an atypical or second generation antipsychotic agent. Its use has been associated to increase of the QT interval, which might trigger potentially lethal ventricular arrhythmia. We present a case of overdose with moderate doses of the drug, in which there were no important changes in the QT interval. A review of the cases of overdose published up to now was also done.

Key words:
Ziprasidone. Atypical neuroleptics. Overdose. QT interval.

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Intoxicación por ziprasidona: seguridad cardíaca

Ziprasidona es un fármaco neuroléptico de reciente comercialización en España que por su perfil receptorial es considerado de segunda generación o atípico. Su uso se ha asociado a alargamiento del espacio QT, que podría desencadenar arritmias ventriculares potencialmente letales. Presentamos un caso de intoxicación con dosis moderadas del fármaco que no se acompañó de alteraciones importantes del QT y realizamos una revisión de los casos de sobredosis publicados hasta el momento.

Palabras clave:
Ziprasidona. Neurolépticos atípicos. Sobredosis. Intervalo QT.

Ziprasidone is a neuroleptic drug recently sold in Spain. It is included in the group of atypical antipsychotic agents due to its action mechanism (serotonin and dopamine blockage)[1].

One of the subjects dealt with most regarding its introduction into the market has been its safety profile, specifically the possibility of slowing down the cardiac conduction, prolonging the QT interval of the electrocardiogram, with the consequent risk of torsade de pointes ventricular arrhythmias. It is considered that the normal values of the QTc interval should not exceed 425 msec in adolescents and adults, 440 msec in children and 450 msec in children under six years old[2].

Safety in the case of overdose, an event that may frequently occur in psychiatric patients, takes on special importance within this risk. We have found four cases of overdose in the review that we have performed.

In the first[3], the case of a 50 year old male patient seen at 4 and a half hours of the overdose due to 3.120 mg of ziprasidone is described. On examination, he had a Glasgow of 15 and blood pressure 200/95. The ECG showed mild prolongation of QTc (490 msec) and non-specific abnormality of the T wave, which was maintained in the next six hours of monitoring and symptomatic treatment, after which it became normal.

House[4] reported the case of a 38 year old female patient who suffered overdose with 4,020 mg of ziprasidone, without symptoms on the first evaluation (one hour after intake). Her ECG showed sinus rhythm. At 6 hours of the dose, she showed delay in conduction, with QRS of 111 msec, QTc of 445 msec, alternating somnolence and agitation with blood pressure 99/34. She also suffered diarrhea and urinary retention. The picture resolved in 14 h.

In another case, Biswas et al.[5] described intoxication due to overdose with 2,400 mg of ziprasidone and 2,250-3,000 mg of bupriopion by a 17 year old male patient. He was seen at one hour of intake, drowsy, but responding to verbal stimuli, and he entered into a lethargic state that required intubation at 45 min. Two and a half hours after, the patient had an increase of QRS (200 msec), which resolved with lidocaine, and the QRS was 120 msec and QTc 480 msec at 12 h. He was admitted with cardiac monitoring and antiarrhythmic treatment, 80 h being necessary for stabilization. Since both drugs are potentially cardiotoxic, it is not easy to attribute these abnormalities to one or the other, or to a synergic effect.

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In a recent article, Teich[6] reported the case of a 52 year old female patient who suffered a confusional episode due to iatrogenic hypopotassemia one month after discontinuing treatment with ziprasidone. Due to the hypopotassemia, she spent an undefined number of days taking the previous regime of ziprasidone. Finally, she was seen in the emergency service for a stuporous picture, where an ECG was performed. It showed sinus rhythm of 75 beats per minute, QTc between 680 and 720 mec, PR of 166 and QRS of 92, with axis slightly shifted to the right. Potassium and magnesium levels in blood on admission were 1.8 mEq/l and 2.4 mEq/l, respectively. The ions and electrocardiogram became normal with serum therapy, achieving the resolution of the picture.

In the premarketing studies, which included more than 5,400 patients and healthy individuals, ten cases of voluntary intoxications were documented. Maximum dose taken was 3,240 mg, the patients having minimum sedation, dysarthia and transitory hypertension (200/95 mmHg). In every cases, the patients recovered without sequels[7].

We present the case of a 31 year old male patient diagnosed of mixed personality and toxic abuse disorder, with background of several short psychotic pictures. He has been receiving treatment with 180 mg/day of ziprasidone and 225 mg of Venlafaxine since nine months ago. Due to the imminence of legal problems, the patient took 13 60 mg tablets of ziprasidone (780 mg) to commit suicide, going to his health center one hour later requesting evaluation. In this first examination, no symptoms were found, but he was referred to the reference hospital for a more extensive evaluation.

On reaching the hospital (90-120 min after intake), the patient reported mild somnolence, without finding other signs in the examination. Glasgow was 15, cardiopulmonary auscultation was normal, blood pressure was 135/71 and heart rate 100 beats per minutes. The electrocardiogram (fig. 1) showed sinus rhythm at 100 beats per minute, without abnormalities in the axis or in repolarization. QTc was 350 msec and PR 200 msec.

Gastric lavage was performed, there still being drug remains. Serum therapy, oxygen therapy and supply of potassium chloride were prescribed and he went to the observation ward with serum therapy and heart monitoring. A complete blood count, hepato-renal biochemistry and urine analysis were performed and were normal. Toxic screening in urine was negative.

At 24 h, the patient was discharged to Internal Medicine, without having any electrocardiographic abnormalities during his stay in observation. After assessment by the psychiatrist on duty, the patient was discharged to continue out-patient treatment.

At 48 h of the intake a control out-patient electrocardiogram was performed (fig. 2). Sinus rhythm at 90 beats per minute was observed without abnormalities in the axis or in repolarization, the QTc was 370 ms and PR 200 ms.

Although ziprasidone may increase the QTc interval, no relationship was found between this prolongation and appearance of torsades de pointes[8]. In case of overdose, the action to follow would include respiratory support, ECG and

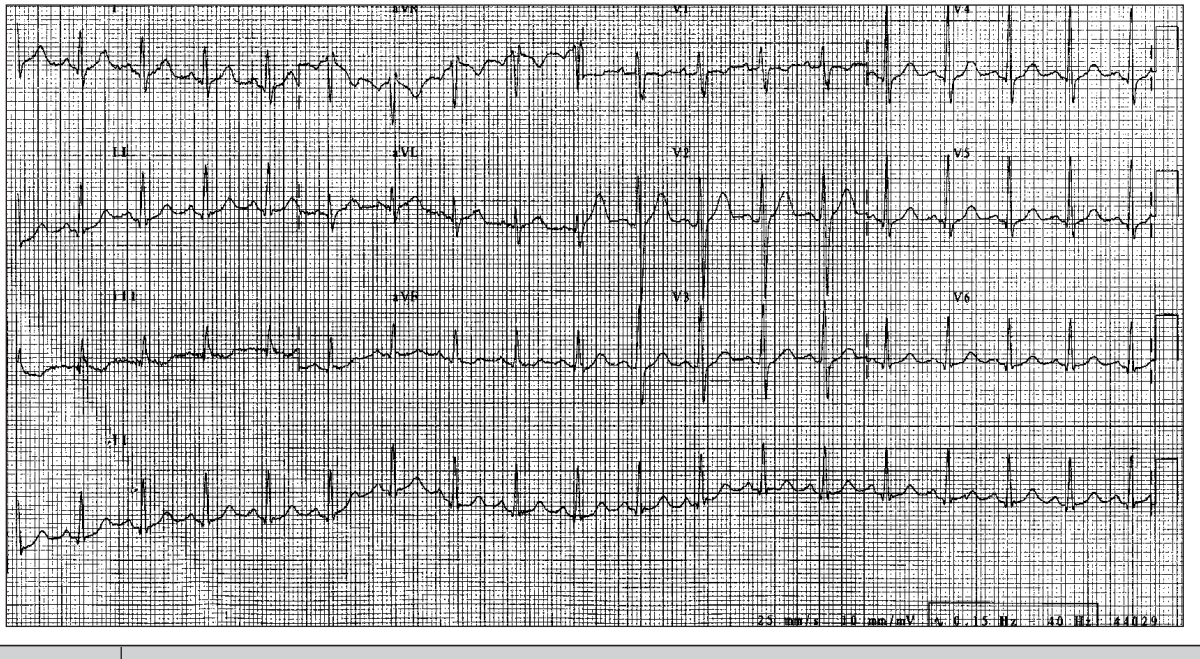

Figure 1 *ECG at 2 h after intake.*

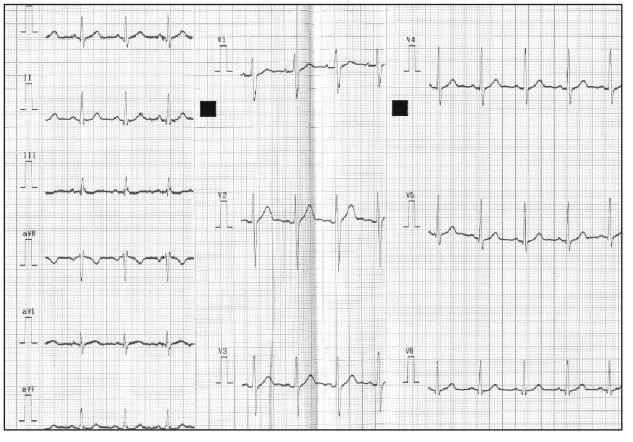

Figure 2 *ECG at 48 h after intake.*

hemodynamic constants monitoring, symptomatic treatment of abnormalities and attention to appearance of delusion and anticholinergic effects. It must be considered that the plasma peak is reached at 4-6 h of the intake, so that careful observation should be extreme at least until this time. The care should be greater if there is a background of heart disease or if the patient has taken any other drug that also affects cardiac conduction.

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