

## Death connected to paralytic ileus due to the intake of antipsychotic drugs. *Case report*

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**Abstract:** The aim of this article is to enlarge furtherly the case-studies on the potentially lethal side-effects of second generation atypical antipsychotic drugs. We report the case of a 40-years-old man, under treatment with quetiapine and clozapine because of a psychotic upset, presenting persistent constipation, who died few hours after his arrive at the ER. The autopsy, together with toxicological and histologic exams, allowed to hail the cause of the death from a cardiac upset, fostered by hydroelectric imbalance connected to the sub-occlusion context. This evaluation has been related to the side-effects of these drugs – even if used with therapeutic dosages – that are able to cause in predisposed people, the onset of disorder within the cardiac rhythm, provoking ventricular fibrillation and death. Because of this reason, a constant patients' monitoring – from the first treatment administration through all the therapy – is beneficial, to prevent the onset of these potential lethal episodes.

**Key Words:** second generation atypical antipsychotics, intestinal sub-occlusion, prolongation of QT interval.

Life expectancy for patients afflicted with mental pathologies – even under pharmacological therapy – is lower than healthy people. Apart from suicides, the death rate has increased of about 20%, both for the poor compliance to the therapy and the life-style (inactiveness, obesity) [1], but also because of the frequent use of stimulant substances (smoke and alcohol). Furthermore, the same drugs used as chronic therapy can provoke death, that in the most of case depends from cardiovascular disturbs [2].

Among the drugs most used as long-term treatment of psychotic disorders there are the second generation atypical antipsychotic medications, since they have less motor side-effects [3]. However, also these drugs have several anticholinergic side-effects such as

xerostomia, mydriasis, increasing of body temperature, and constipation. The latter often is reported, but at the same time it is underrated, becoming one of the possible causes of death when it is so serious to cause an intestinal sub-occlusion due to paralytic ileus [4].

Another potentially detrimental side-effect is the prolongation of QT interval, responsible, in turn, of torsade de pointes that can cause sudden death by ventricular tachycardia [5].

This article refers to the death of a subject, under chronic treatment with quetiapine and clozapine for several years because of a no detailed psychosis, who presented two of the main side-effects of the therapy: constipation complicated by intestinal sub-occlusion and cardiac disorders.

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## CASE REPORT

A 40-years-old man died during the night at his house, after have been dismissed by an ER where he went reporting abdominal aches and constipation (the latter lasting from twenty days), that didn't get better in spite of the usage of laxatives. The case history gathered at the ER reported the man was suffering from a no-detailed psychosis and because of that he was under domestic treatment as follows: pills of quetiapine (200mg x 2 + 300mg in the evening) and clozapine drops (100mg/ml, 15 drops in the evening). During the objective exam, doctors noted: globular abdomen, treatable, no painful during palpation, negative Blumberg, torpid peristalsis, neoformed excrements inside phials. The X-Ray of abdomen highlighted: *"...rough hydroaereous level of transverse colon. Abundant faecal remainders within the lower abdominal quarters"*. Hence, a constipation was diagnosed, with the resulting prescription of a therapy focused on laxatives (syrup of lactulose), evacuative enemas, hydration and feeding by fibers and vegetables, plus regular check-ups with his physician.

According to what was reported by his relatives, after the ER discharge, the men came back at his place and retired without eating. The following morning, he was found dead.

The obtained medical documentation confirmed that the man was in treatment at a psychiatric structure. An ECG exam was also enclosed, showing a block in the right branch.

Examining externally the body, it had a normal complexion (height, weight), with an increased abdominal volume.

The autopsy detected, besides a scattered polivisceral congestion and pulmonary edema, some elements at intestinal meanders level, which were very extended and distended, especially the transverse and falling colon. The small intestine had a circumference of 6 cm starting from duodenum, for at least 120 cm length. Also the big intestine presented an increased volume, 40 cm circumference at rising and transverse colon, 35 cm at falling colon, 28.5 cm at sigma level and 19 cm at rectum. The total weight of colon and its content was 9 Kg. Within the stomach there were about 240 ml of



**Figure 1.** In the box at the top right: small intestine with a circumference of 6 cm starting from duodenum, for at least 120 cm length. In the boxes at the bottom: the big intestine presented an increased volume.

dark fluid, with a fecal aspect and odour, with a mucosa presenting ipereremia areas, more packed in the bottom of the stomach and near a small flexing. Within the small intestine some intestinal material was detected (400 ml), fluid in the first section, more firm after; the mucosa showed a diffused ipereremia. Opening the colon, faecal material was evident, concentrated mainly in the rectum (faecaloma) and with the ipereremia mucosa, in the rectum most of all.

The volume of the liver was increased (2600 g); it was congested and steatotic.

The histologic exam showed: several seed-beds of sub-endocardial fibrosis, with major adipose infiltrations by the right ventricle, besides the evidence of nonspecific chronic inflammation of intestinal walls.

The toxicological exam reported the presence of quetiapine traces within the blood and urine, and also of its metabolite N-demetilquetiapine in the blood (1 µg/ml). Also the other active principle, clozapine, was present in the blood and urine, with its metabolite N-demetil-clozapine (0.1 µg/ml).

## DISCUSSION

The available data permitted to establish that the death was due to sudden cardiac death, depending from an hydroelectric disorder caused by paralytic ileus.

From at least 10 years, the subject was used to follow a pharmacological antipsychotic therapy through second generation neuroleptics, Clozapine and Quetiapine, able to cause constipation and even cardiac disorders - prolonging the QT interval - and fatal ventricular arrhythmia.

The scientific literature reports several cases that describe the side-effects of antipsychotic drugs in their users, such as the extension of QT interval [6-7] and constipation.

Talking about the first complication, initially it was thought that only first generation antipsychotic drugs caused it; but then, many advisories were reported of a prolonging of QT interval even with the second generation drugs [8], such as quetiapine and clozapine [9].

From a physiopathology point of view, the mechanism by which these drugs modify the electrical myocardium conductivity can be connected to the similarity among the subunits forming the ionic channel, that can cause disorders in the conduction during an ECG exam (just

like in the case here reported), and even fatal arrhythmia.

Referring, instead, to constipation, literature reports its predominance in people using antipsychotic drugs, with variable, but similar rates. Potkin *et al.* [10] have noticed an its preponderance by 12% (considering 156 patients), while a study carried out with Korean psychiatric patients following therapy with quetiapine, constipation was observed in 9.6% of the cases [11].

Constipation, if persistent and underrated or not treated adequately, can lead to a block of peristalsis or even to paralytic ileus with fatal consequences [12-14].

Hence, also the indications provided by literature compared with our case-evidences allowed to confirm a connection between the side-effects of pharmacological therapy and the death.

The histological context was compatible with the morphological characteristics of a potential arrhythmogenic circuit because of the presence of multiple subendocardial fibrosis centers and adipose substitution, possible points of cardiac conduction interruption and chaotic propagation of electric pulses; this context was fostered by disorders of the functioning of cellular ionic channels, generated by the use of antipsychotic drugs [15].

These histological disorders (subendocardial, interstitial and subepicardial fibrous and adipose substitution) are an histopathologic evaluation often connected in the literature with sudden cardiac death [16].

Furthermore, the disorder of electric conductivity was fostered by electrolytic changes (especially in the serum potassium) due to intestinal sub-occlusion [17].

## CONCLUSION

We have here presented a case to confirm the dangerousness of some side-effects - even very common - of chronic therapies using second generation neuroleptic drugs, such as clozapine and quetiapine. It is advisable that patients under treatment with these drugs are constantly clinically monitored. Most of all, it is right and proper to put every single patient through an ECG exam before starting the therapy, and during its implementation; a special attention should be paid towards those patients presenting specific risk elements (personal or familiar) for cardiovascular diseases [18].

## Conflict of interest

We declare that there is no conflict of interest.

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