

Cardiac adverse reactions associated with psychotropic drugs

Rates of cardiovascular morbidity and mortality in psychiatric patients are higher than in the general population: it is estimated that those who suffer from schizophrenia have a life expectancy approximately 20% shorter than those who do not, and this difference is not fully accounted for by suicide or accidental death.¹ Cardiovascular adverse effects of psychotropic drugs are common, and potentially harmful.² The most serious cardiovascular consequences of psychotropic drugs are arrhythmias and sudden death, which principally result from torsades de pointes following progressive QT interval prolongation. Less severe cardiac adverse drug reactions are extremely common. Orthostatic hypotension, vasodilatation with transient collapse, and reflex sinus tachycardia due to α_1 -adrenoceptor blockade and to anticholinergic effects occur at therapeutic dosages of several psychotropic drugs. Postural hypotension was found in 77% of patients receiving antipsychotic medication versus 15% receiving placebo, and a correlation was found with drug dosage.³ Furthermore, antipsychotic drug use is associated with an increased risk of hip fracture with a relative risk of 2 (confidence interval [CI], 1.6 to 2.6) and accounts for a third of all falls in nursing homes.^{4,5}

Sudden death

A 10-year cohort study found a 1.33-fold relative risk of death in a schizophrenic population compared with a control population; the leading cause of death was cardiovascular disease.⁶ In patients with myocardial infarction and cardiac failure, reduced heart rate variability is one of the predictive factors of increased risk of cardiac death⁷; this reduced heart rate variability might be due to the anticholinergic effects of psychotropic drugs.⁸ Polymedication was also identified as an independent risk factor for death.⁶ Thioridazine, an old and widely prescribed neuroleptic drug which was recently withdrawn, was associated with 75% of 49 deaths in a patient group taking a single antipsychotic drug regimen; its potential for QT prolongation had already been reported in 1963.^{9,10} Unexplained sudden death in young adults has been linked to the prescription of antipsychotics other than thioridazine.¹¹

QT interval

Electrocardiographic modifications due to psychotropic drugs include prolongation of the PQ interval (atrioventricular blocks of different degrees of severity), widening of the QRS interval (bundle branch block), ST-segment changes (repolarization disturbances), and prolongation of the QT interval.

Drug-induced long QT syndrome is an underestimated adverse drug effect: morbidity and mortality associated with a prolongation of the QT interval currently constitute the most frequent cause of drug withdrawal from the market or “black-box” warning after marketing.¹² In 1920, Bazett found that the repolarization phase was related to ventricular systole, and that its duration was mainly influenced by the heart rate.¹³ Bazett's formula corrects the QT interval with an approximation for a rate of 60/min as follows: $QT_c = QT / \sqrt{RR}$, expressed in seconds (*Figure 1*).

Prolongation of the QT interval is considered to be a surrogate marker for the risk of developing a particular type of ventricular tachyarrhythmia called “torsades de pointes” (TdP), which may be recognized on the electrocardiogram (ECG) as a twisting of the QRS axis (*Figure 2*). TdP results in malaise, syncope, and cardiac arrhythmic death by ventricular fibrillation.

Prolongation of the QT interval was reported in 8% of 495 psychiatric inpatients.¹⁴ In an unpublished study in 1000 inpatients under 65 years of age, the most frequently detected major ECG modification at admission was QT prolongation. Serious cardiac events and sudden death occurred more often at high doses of haloperidol, droperidol, sertindol, and methadone^{15,16}; hence, drug-induced QT interval (repolarization phase) prolongation is mainly considered as a dose-dependent adverse reaction.

Effects on ion channels

Psychotropic drugs block several potassium currents (eg, I_{Ks} and I_{Kr}) during repolarization (phases 2 and 3 during the action potential), resulting in a prolonged QT interval on the ECG with an increased risk of developing TdP. Similarly, eight phenotypes of the congenital long QT syndrome are recognized. The most frequent phenotypes are for potassium channels $KCNQ1$ (or $KVLQT1$) coding *long QT type 1* (LQT_1) and $KCNH2$ coding LQT_2 ; for sodium channels, $SCN5A$ is responsible for the LQT_3 phenotype. Drugs such as methadone, amitriptyline, haloperidol, and sertindole promote QT prolongation by blocking the *HERG* potassium channels.^{16,17} As for class Ic antiarrhythmic drugs, such as flecainide and prope-

fanone, haloperidol also blocks sodium channels, and displays a quinidine-like effect by slowing sodium influx into myocytes.¹⁸

All drugs enhancing the QT interval prolongation should not be prescribed in patients with congenital long QT. Furthermore, several psychotropic drugs block in vitro calcium channels of the L-type and may cause bradycardia and heart block through negative inotropic effect.

In contrast to low-voltage calcium ion channels (T-type) located in pacemaker cells, high-voltage channels of the L-type modulate conduction through the sinoatrial pathway and the atrioventricular node. This mechanism may explain the unusual occurrence of second-degree sinoauricular (Mobitz type II) or atrioventricular block during clozapine prescription (*Figure 3*). Moreover, atrial fibrillation is also reported as an unusual adverse reaction during clozapine treatment.¹⁹

Inherited defects of ion channels responsible for congenital long QT syndrome (which are not always apparent on the ECG), polymedication, methadone maintenance, hypokalemia, hypomagnesemia, and history of cardiovascular disease are risk factors that increase the clinical consequences of the ion-channel effects of psychotropic drugs.¹⁶ However, age as a single factor does not seem to contribute substantially to the risk of cardiac adverse drug reactions.²⁰

Dose-independent adverse reactions

Besides the QT interval prolongation and other major ECG modifications such as atrioventricular block and intraventricular conduction delay of different degrees of severity, other serious cardiovascular adverse reactions which are not dose-dependent are associated with psychotropic drugs. Several deaths, from myocarditis and cardiomyopathy during clozapine therapy were reported in physically healthy young adults.^{21,22} The WHO database

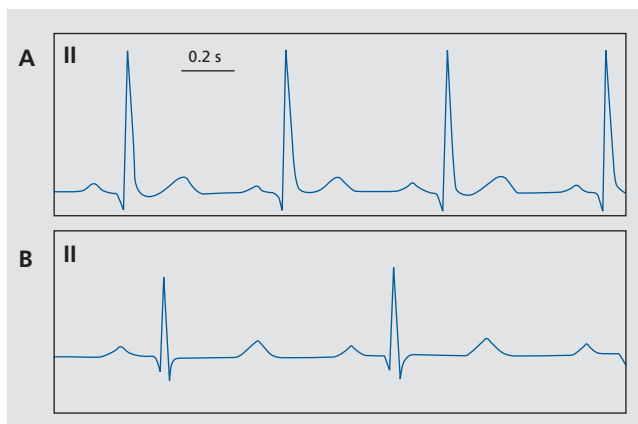


Figure 1. Prolonged QT interval. A, QT interval: 0.28 sec, RR: 0.60 sec, QTc: 0.36 sec; B, QT interval: 0.47 sec, RR: 0.88 sec, QTc: 0.50 sec.

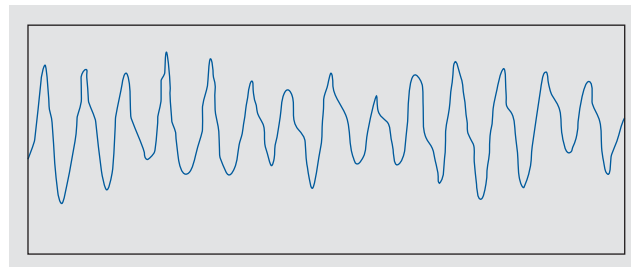


Figure 2. Torsades de pointes. The ECG tracing shows characteristic twisting of the QRS axis. ECG, electrocardiogram

Poster

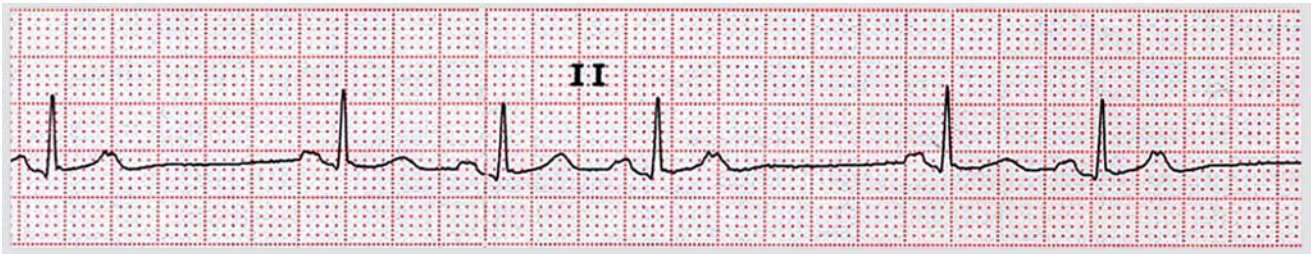


Figure 3. Second-degree atrioventricular block (Mobitz type II) in a schizophrenic patient 6 days after clozapine initiation 100 mg bid with positive dechallenge and normal sinus rhythm 2 days after clozapine cessation (dechallenge not shown).

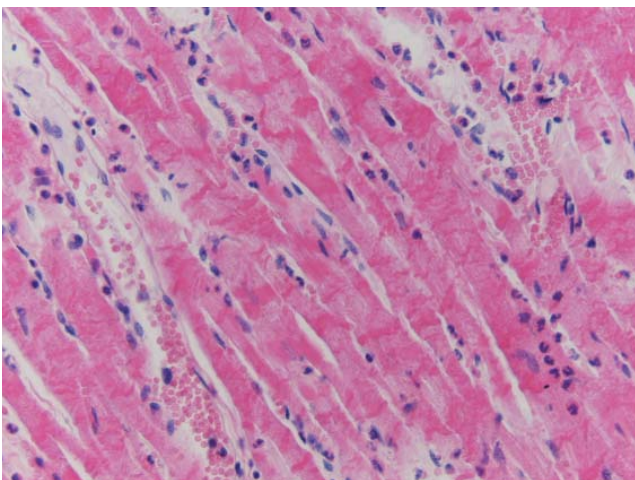


Figure 4. Acute myocarditis 8 days after clozapine treatment initiation: histopathological pattern. Cardiac tissue of a 18-year-old woman with myocytolysis, diffuse eosinophilic and lymphocytic infiltrates. The etiology seems to be clearly of immunological or hypersensitivity reaction rather than of pharmacodynamic cause. Photo courtesy of Prof P. Mangin and Dr M. Bollmann, Forensic Pathology, Lausanne.

shows that clozapine is significantly more frequently reported in relation to cardiomyopathy and myocarditis (Figure 4) than other drugs.²³ Myocarditis and cardiomyopathy were also associated with chlorpromazine, lithium, fluphenazine, risperidone, and haloperidol, but these associations need to be further investigated in order to establish whether they are causal.

Discussion

The above information indicates that ECG monitoring should be performed during hospitalization and ambulatory treatment, at least when multiple psychotropic drug regimens, methadone maintenance treatment, and other predisposing factors for QT prolongation are present at admission.

We particularly recommend regular cardiac and ECG monitoring in patients receiving clozapine, high-dosage antipsychotics, tricyclic antidepressants, drug regimens with potential interactions, or in clinical situations recognized as promoters of QT prolongation. Further electrocardiographic studies in psychiatric patients, systematic recording of case reports, and data mining in pharmacovigilance systems will help establish the magnitude of cardiac adverse reactions to psychotropic drugs. □

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