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Review Article

Drug-induced block of cardiac HERG potassium channels and development of *torsade de pointes* arrhythmias: the case of antipsychotics

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Abstract

The prolongation of the cardiac repolarization process, a result of the blocking of the Human Ether-a-go-go Related Gene potassium channel, is an undesired accessory property shared by many pharmacological classes of non-cardiovascular drugs. Often the delayed cardiac repolarization process can be identified by a prolongation of the QT interval of the electrocardiograph. In these conditions, premature action potentials can trigger a dangerous polymorphic ventricular tachyarrhythmia, known as *torsade de pointes*, which occasionally can result in lethal ventricular fibrillation. In this work, brief descriptions of the electrophysiological basis of *torsade de pointes* and of the several pharmacological classes of torsadogenic drugs are given. Attention is focused on antipsychotics, with a deeper overview on the experimental and clinical reports about their torsadogenic properties.

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The cardiac action potential

Cardiac action potentials are generated by trans-membrane movements of ion species, flowing principally through specific channels. In a typical human cardiac action potential (Figure 1A), five different phases can be recognized. Phase 0 is a rapid depolarization process resulting from a massive inward flow of Na^+ (current I_{Na}). The following phase 1 is linked to the inactivation of the I_{Na} current and to a weak and transient repolarization due to an outward flow of K^+ (current I_{to}). Phase 2 reflects an almost iso-electric plateau generated by the simultaneous activation of a depolarizing inward Ca^{++} current, a repolarizing outward rapidly activated K^+ current (current I_{Kr}) and a repolarizing outward slowly activated K^+ current (current I_{Ks}). Phase 3 reflects the complete membrane repolarization due to many K^+ currents (mainly I_{Ks} and I_{Kr}), which leads the cell to the recovery of resting membrane potential. Finally, phase 4 is the resting period, ensured by inward rectifier K^+ currents (I_{K1}), before a new following cardiac cycle.

The QT interval

A typical electrocardiograph (ECG) tracing of a human cardiac cycle (Figure 1B) starts with a P wave (80–110 ms) representing the atrial depolarization. The following iso-electric time (about 100 ms) reflects the propagation of the depolarization through the atrio-ventricular node to the ventricular conduction system. The QRS complex (< 120 ms) represents the whole ventricular depolarization, followed by an isoelectric time (about 120 ms) starting from the J point. Finally, the T wave (230–300 ms) represents the final ventricular repolarization and the end of the cycle. Among the various ECG parameters that are useful in analysing the cardiac functions, the QT interval is the most usual one for estimating the ventricular repolarization process.

Drug-induced *torsade de pointes*

Many drugs belonging to different pharmacological classes (Table 1) can trigger life-threatening polymorphic ventricular tachyarrhythmias, such as *torsade de pointes*. In particular, many non-cardiovascular drugs in common clinical use cause the prolongation

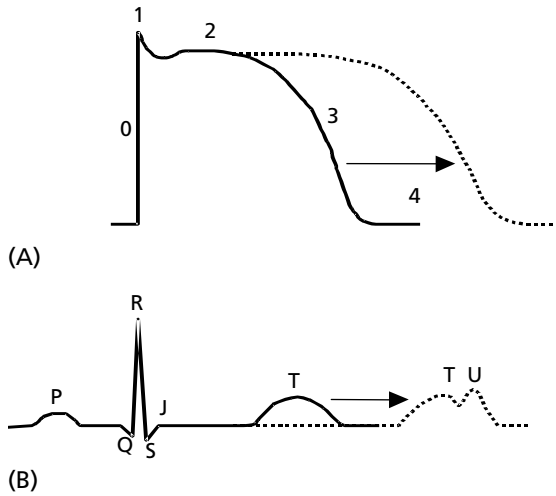

Figure 1 (A) The five phases of a typical human cardiac action potential. (B) ECG tracing of a human cardiac cycle. The dotted lines show the effects of torsadogenic drugs: the prolongation of the cardiac repolarization process and the prolongation of the QT interval of the ECG, with the possible presence of an anomalous U wave.

of the cardiac repolarization process, independently from their main pharmacological mechanism of action (Figure 1).

Generally, premature action potentials, which stop the repolarization process, trigger *torsade de pointes* events. Often, they are preceded by the prolongation of the QT interval, alternating long–short–long cardiac cycles and

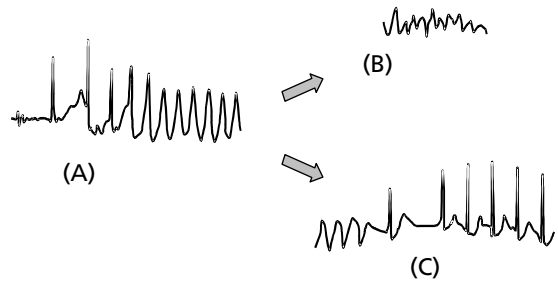

Figure 2 (A) ECG tracing during an episode of *torsade de pointes* that can precipitate into ventricular fibrillation (B) or spontaneously recover the sinusal rhythm (C).

anomalous U waves, surmounting the T wave, and are characterized by wide and morphologically aberrant QRS complexes, oscillating around the isoelectric line of the ECG tracing (Figure 2A).

Torsade de pointes can be followed by a spontaneous recovery of the sinus-rhythm or, rarely, can precipitate into a lethal ventricular fibrillation (Figures 2B and C). In these arrhythmogenic events, a pivotal role is played by potassium channels. The most frequently involved is the potassium rapid delayed rectifier (K_r) channel, encoded by the Human Ether-a-go-go Related Gene (HERG) gene, known as the HERG channel: drugs blocking the HERG channel can induce *torsade de pointes* events.

Although *torsade de pointes* represents a very rare event in patients with a normal repolarization reserve (due to the multiple K^+ currents allowing the recovery of a complete

Table 1 List of drugs with torsadogenic properties

Pharmacological class	Drugs
Antiarrhythmic	N-Acetylprocainamide, almokalant, amiodarone, aprinidine, azimilide, clofilium, disopyramide, dofetilide, E-4031, encainide, flecainide, ibutilide, LY 97241, mexiletine, MK-499, procainamide, quinidine, RP-58866, D-sotalol, terikalant, WAY-123,398
Antianginal	Bepridil, perhexiline, ranolazine
Antihyperthensive	Amlodipine, captopril, carvedilol, diltiazem, isradipine, ketanserin, mibefradil, moexipril, nicardipine, nifedipine, nitrendipine, propranolol, trimethaphan, verapamil
Antidepressant	Amitriptyline, citalopram, clomipramine, desipramine, doxepine, fluoxetine, imipramine, maproptiline, nortriptyline, paroxetine, sertraline, trazodone, venlafaxine, zimelidine
Antipsychotic	Chlorpromazine, clozapine, droperidol, flufenazine, haloperidol, lithium, mesoridazine, olanzaipine, pimozide, quetiapine, risperidone, sertindole, sultopride, thioridazine, trifluoperazine, ziprasidone
Antihistamine	Astemizole, cetirizine, chlorpheniramine, cyproheptadine, DC-loratidine, desmethylastemizole, diphenhydramine, ebastine, epinastine, fexofenadine, loratadine, mizolastine, norastemizole, pyrilamine, terfenadine
Antibiotic/anti-infective	Amantadine, amphotericin, azithromycin, ciprofloxacin, clarithromycin, clindamycin, erythromycin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, pentamidine, sparfloxacin, spiramycin, telythromycin
Anticancer	Arsenic trioxide, doxorubicin, tamoxifen, zorubicin
Antimycotic	Clotrimazole, fluconazole, ketoconazole, itraconazole, miconazole, voriconazole
Antimalarial	Chloroquine, halofantine, quinine
Others	Atropine, cisapride, chloral hydrate, cocaine, cromakalim, domperidone, felbamate, foscarnet, fosphenytoin, glibenclamide, granisetron, indapamide, levomethadil, methadone, naratriptan, octreotide, ondansetron, OPC-18790, Probucolo, salmeterol, sildenafil, spironolactone, sumatriptan, tacrolimus, terodiline, tizanidine, valproic acid, vesnarinone, zolmitriptan

Table 2 Risk factors associated with *torsade de pointes* events

Female gender
Electrolyte imbalance (hypokalaemia, hypocalcaemia, hypomagnesaemia)
Heart disease
Bradycardia
History of congenital long QT syndrome
Age
Drug synergism (pharmacodynamic interaction)
Co-consumption with CYP3A4 inhibitors (phamacokinetic interaction)

and rapid repolarization, also in the presence of disturbing factors), this arrhythmia can be dramatically facilitated when some risk factors that involve a reduced repolarization reserve are present (Table 2) (Tamargo 2000).

The occurrence of *torsade de pointes* with non-cardiovascular agents persuaded the Committee for Proprietary Medicinal Products (1997) to issue a *Points to Consider* document proposing detailed considerations on pre-clinical and clinical methods for determining the cardiac electrophysiological safety of non-cardiovascular medicinal products.

Non-cardiac drugs

A definitive list of torsadogenic drugs is not available to date because new experimental and/or clinical data force constant updates. However, many non-cardiovascular drugs that cause *torsade de pointes* and/or QT-prolongation are shown in Table 1. Briefly, they can be grouped into some major and heterogeneous pharmacological classes.

Antihistamines
Some antagonists of the H_1 histamine receptor, such as astemizole and terfenadine, which belong to the second generation (i.e. are devoid of sedative effects), can block the HERG channel, causing a decrease in the I_{Kr} current and QT prolongation. In the scientific literature, cases of *torsade de pointes* have been associated with these drugs.

Antimycotics
Ketoconazole shows HERG-blocking properties. Moreover, it and related molecules (fluconazole, miconazole and itraconazole) can also potentiate the arrhythmogenic toxicity of torsadogenic drugs through the inhibition of the enzymatic system (i.e. the isoform CYP3A4 of the cytochrome P-450), which is responsible for the biotransformation and detoxification of these drugs.

Antibiotics
High blood concentrations of the macrolide antibiotics erythromycin and clarithromycin block the I_{Kr} current and alter the cardiac repolarization process. Furthermore, they can inhibit CYP3A4, increasing the danger associated with the use of other torsadogenic agents. Fluoroquinolonic antibiotics, such as sparfloxacin and grepafloxacin, can also prolong the QT interval and induce *torsade de pointes*.

Antidepressants
Cases of *torsade de pointes* associated with the use of imipramine, desipramine and doxepine have been reported. Furthermore, the ability to prolong the QT interval has been recognized in other antidepressants, such as venlafaxine (Gralinski 2000; Tamargo 2000).

Antipsychotic drugs

Antipsychotic drugs represent a heterogeneous chemical group of compounds whose therapeutic efficacy often derives from their interaction with dopamine receptors and/or serotonin receptors. The typical (first-generation) antipsychotics (1950–1990) have been the major pharmacological agents in the treatment of schizophrenia but their therapeutic effects are coupled with negative symptoms, including extrapyramidal syndrome, tardive dyskinesia and hyperprolactinaemia. These effects reduce the compliance of these drugs. The atypical (second-generation) antipsychotics, introduced in 1990, produce a lower incidence of extrapyramidal effects and hyperprolactinaemia.

The use of large doses of psychoactive agents, of either first or second generation, can be associated with alterations of cardiac repolarization and cases of *torsade de pointes* (Table 3). In the literature there is considerable evidence that psychiatric patients present a higher risk of sudden death independent from a specific pharmacological treatment; a study by Warner and collaborators (1996) showed an increase in the QT interval in psychiatric patients associated with a high dose of drugs (Food and Drug Administration 2000a).

Phenothiazines
An early examination by Ban and Stjean (1964) evidenced the link between phenothiazine drugs and ECG abnormalities: patients treated with both chlorpromazine and thioridazine showed QT prolongation, which normalized when the drug was discontinued.

In 1963 two reports of sudden deaths were associated with thioridazine treatment. The first was a 46-year-old woman who received this antipsychotic in doses of between 600 and 3600 mg day^{-1}. She developed cardiovascular collapse and died (Kelly et al 1963). Subsequently, in 1968 a young man (19 years old), who was taking thioridazine, died following an increased QT interval (650 ms) (Giles & Modlin 1968).

Between 1980 and 1981 four patients in therapy with phenothiazines were admitted to hospital with syncope or ventricular fibrillation. The *torsade de pointes* events always followed a QT interval prolongation (Ko et al 1982). Another case of phenothiazine-induced *torsade de pointes* has been described in a schizophrenic patient (Wilson & Weiler 1984).

A dangerous association between phenothiazine and diuretic drugs has also been reported, in particular a 54-year-old woman had recurring syncope events caused by phenothiazine treatment and hypokalaemia caused by chlortalidone therapy (Jarchowsky et al 1991).

Table 3 References for experimental and/or clinical evidence of torsadogenicity

Drug	References for torsadogenicity evidence	
	Experimental	Clinical
Phenothiazines		Ban & Stjean 1964 Giles & Modlin 1968 Jarchowsky et al 1991 Kelly et al 1963 Ko et al 1982 Wilson & Weiler 1984
Thioridazine	Drolet et al 1999 Hamlin et al 2004 Kongsamut et al 2002 Studenik et al 1998 Testai et al 2004	Basteaky et al 1990 Donatini et al 1992 Hulisz et al 1994 Liberatore & Robinson 1984 Raehl et al 1985
Chlorpromazine	Studenik et al 1998 Thomas et al 2003	Ochiai et al 1990 Warner et al 1996
Butyrophenones		Lawrence & Nasraway 1997
Haloperidol	Drici et al 1998 Hamlin et al 2004 Lande et al 2001 Osypenko et al 2001 Suessbrich et al 1997 Sugiyama et al 2003 Testai et al 2004	Fayer 1986 Glassman & Bigger 2001 Hatta et al 2001 Henderson et al 1991 Hunt & Stern 1995 Kriwisky et al 1990 Nagaraja et al 1998 O'Brein et al 1999 Perrault et al 2000 Su et al 2003 Tisdale et al 2001
Droperidol	Adamantidis et al 1994 Drolet et al 1999	Dershwitz 2002 Guy et al 1991 Lischke et al 1994 Michalets et al 1998
Dibenzazepines	Kongsamut et al 2002	
Clozapine	Drici et al 1998	Grohmann et al 1989 Kang et al 2000 Klimke & Klieser 1994 La Grenade et al 2001
Olanzapine	Drici et al 1998	Czekella et al 2001a,b Dineen et al 2003 Gurovich et al 2003
Quetiapine	Duffy et al 2001	Frust et al 2002 Gajwani et al 2000 Gupta et al 2003 Harmon et al 1998 Nudelman et al 1998 Pollak & Zbuk 2000 *Physician's Desk Reference* 2000a,b
Benzamides		
Sulpiride	Sugiyama et al 2002	Su et al 2003 Sugiyama et al 2002 Takeda et al 2001
Sultopride	Adamantidis et al 1994 Lande et al 2001	Lande et al 1992 Montez et al 1992
Others		
Pimozide	Drolet et al 2001 Finlayson et al 2001 Kang et al 2000 Osypenko et al 2001	Committee on Safety of Medications – Medical Control Agency 1995 Desta et al 1999 Krahenbuhl et al 1995
Risperidone	Adamantidis et al 1994 Drici et al 1998 Gluais et al 2002 Kongsamut et al 2002	Ravin & Levenson 1997 Titier et al 2002
Sertindole	Drici et al 1998 Eckardt et al 2002 Kongsamut et al 2002 Rampe et al 1998	Fritze & Bandelow 1998 Lewis et al 2000 Mack et al 2002 Food and Drug Administration 1996 Wilton et al 2001
Thiapride		Iglesias et al 2000 Hunt & Stern 1995 Sharma et al 1998 Wilt et al 1993
Ziprasidone	Kongsamut et al 2002	Biswas et al 2003 Burton et al 2000 House 2002 Teasdel & Jannet 1974 Teich 2003

Two parallel studies by Donatini et al (1992) and Warner et al (1996) showed that thioridazine and chlorpromazine were responsible for *torsade de pointes* events in predisposed patients and when used in high doses (above 800 mg day^{-1} for thioridazine and above 2000 mg day^{-1} for chlorpromazine).

There are several reports of *torsade de pointes* associated with thioridazine use. A woman in lithium and thioridazine treatment manifested a *torsade de pointes* event resulting in sinusal bradycardia with atrio-ventricular (AV) block, QT prolongation and the appearance of a large U wave (Liberatore & Robinson 1984). A 56-year-old man in treatment with thioridazine, trifluoperazine and benztropine was hospitalized after a syncopal episode. ECG monitoring revealed an arrhythmia caused by the antipsychotic therapy (Raehl et al 1985). A 35-year-old woman had a *torsade de pointes* episode about 6 h after the ingestion, with suicidal intention, of a single dose of 500 mg of thioridazine (Basteaky et al 1990). Another woman attempted suicide by ingesting thioridazine (3000 mg) and 60 tablets of acetaminophen plus codeine. She was recovered in semicomatose state, with a third-degree AV block, a marked hypotension and *torsade de pointes* events; however, these problems were resolved within 48 h (Hulisz et al 1994).

In 2000 Novartis Pharmaceuticals Canada Inc. publicly indicated the link between thioridazine use and QT prolongation (with potential *torsade de pointes* events) (www.hc-sc.gc.Ca/hpb-dgps/theraput/zfiles/english/notices/mellaril_e.pdf). The co-consumption of thioridazine with CYP450 inhibitors is contraindicated, as demonstrated by a recent study on 65 European psychiatric patients in treatment with the drug. Fifty-four per cent of these had a QT interval over 420 ms, and the lengthening was correlated both with plasmatic concentration and daily dose of the antipsychotic. Patients with an impaired CYP-activity might therefore be more exposed to the risk of *torsade de pointes*.

In 1990, a case of chlorpromazine-induced *torsade de pointes* (100 mg day^{-1}) was reported in a 31-year-old woman. She was admitted to hospital and the polymorphic ventricular tachyarrhythmia was abolished by i.v. infusion of lidocaine (50 mg), although the QT interval remained prolonged until the interruption of the chlorpromazine treatment. A subsequent re-administration of chlorpromazine (50 mg day^{-1}) again produced a QT prolongation (Ochiai et al 1990).

The clinical evidence for these effects is supported by pre-clinical studies. The study on HERG-K^+ channels transfected into Chinese hamster ovary cells (HERG/CHO) in *Xenopus laevis* oocytes (HERG/XO) and studies on guinea-pig ventricular myocytes and human atrial myocytes showed chlorpromazine- and thioridazine-induced reduction of the I_{Kr} current (Drolet et al 1999; Kongsamut et al 2002; Thomas et al 2003; www.fenichel.net/pages/Professional/subpages/QT/Tables/pbydrug.htm). On isolated Purkinje fibres of guinea-pig, thioridazine, but not chlorpromazine, elicited early after-depolarization (EAD) in hypokalaemia conditions (Studenik et al 1998). On isolated perfused guinea-pig hearts and on anaesthetized guinea-pigs, the ECG recordings confirmed the lengthening of the QT interval produced by thioridazine (Hamlin et al 2004; Testai et al 2004).

Butyrophenones

The literature published from 1966 to 1996 reports 18 cases of conduction disturbances associated with butyrophenone drugs (droperidol and haloperidol). Among these 13 (72%) already had a history of cardiovascular disease. However, the number of available case reports was too small to prove a causal relationship between butyrophenones and adverse cardiovascular effects (Lawrence & Nasraway 1997).

The frequency of sudden deaths associated with haloperidol use is lower than that observed for thioridazine; nevertheless, *torsade de pointes* events can occur at therapeutic doses with either oral or i.v. administration, and in overdose situations (Fayer 1986; Kriwisky et al 1990; Henderson et al 1991; Hunt & Stern 1995; Glassman & Bigger 2001). Among 223 patients receiving i.v. haloperidol, eight developed *torsade de pointes* and they assumed the highest dose in the shortest period (Nagaraja et al 1998). Another study on 30 critically ill patients in haloperidol treatment for delusional agitations unmasked a correlation between QT prolongation and *torsade de pointes* episodes (Tisdale et al 2001).

The case of a 41-year-old woman was described by O'Brein and colleagues (1999). She developed ventricular arrhythmia 55 min after haloperidol injection. The ECG recording showed a QT interval prolongation (610 ms) and a *torsade de pointes* episode. An infusion of magnesium sulfate abolished the ventricular arrhythmia (O'Brein et al 1999). Another episode of *torsade de pointes* not associated with QT prolongation was recorded in a patient anaesthetized with haloperidol for a coronary bypass introduction (Perrault et al 2000).

In 2001 a work on 47 patients in haloperidol therapy was published. They were divided into two groups: an FZ-HAL group (receiving flunitrazepam and haloperidol) and an FZ group (receiving flunitrazepam). Eight hours after injection of the drugs, the FZ-HAL group showed a QT interval longer than that of the FZ group (four patients had a QT interval > 500 ms) (Hatta et al 2001).

There has only been one recent clinical study that did not report an evident correlation between QT prolongation and haloperidol treatment. For 4 weeks the authors observed eventual QT interval changes in schizophrenic patients divided into three groups: drug-free, sulpiride-treated and haloperidol-treated (Su et al 2003).

Outside psychiatry droperidol is used as a pre-anaesthetic agent. In a group of 40 patients treated with injections of droperidol (0.1–0.175–0.25 mg kg^{-1}) to induce the anaesthesia, a dose-dependent increase of QT interval was observed (Lischke et al 1994). In another study on 55 patients, Guy and colleagues noted that 1 min after the injection (0.25 mg kg^{-1}), droperidol prolonged the QT interval in 70% of subjects (Guy et al 1991). Moreover, Dershwitz (2002) reported a list of 19 cases describing adverse cardiac effects after the ingestion of a dose of drug lower than 10 mg. One of these cases regarded a 59-year-old woman in treatment with fluoxetine and cyclobenzapine. She was hospitalized for a surgical operation and before it she received droperidol, but during the surgical procedure she developed a *torsade de pointes* episode that precipitated ventricular fibrillation. After the interruption of cyclobenzapine administration, the QT interval returned to normal values. It was therefore supposed that the *torsade de pointes* episode was provoked by the combination of fluoxetine and cyclobenzapine, and not by droperidol (Michalets et al 1998). Among the 19 cases reported by Dershwitz there are nine cases of death, seven from cardiac arrest (Dershwitz 2002).

In 2001, droperidol manufacturers voluntarily discontinued the distribution of the drug in the UK and in the same year the Food and Drug Administration added a 'black box' warning on the use of droperidol, even at the doses typically used for post-operative nausea and emesis, admitting the association between the drug and cardiac arrhythmias (Committee on Safety of Medicines – Medicines Control Agency 2001; Food and Drug Administration 2001).

Pre-clinical studies revealed the ability of haloperidol to reduce the I_{Kr} current in HERG channels expressed in human embryonal kidney cells (HERG/HEK) and HERG/XO (Suessbrich et al 1997; Osypenko et al 2001; www.fenichel.net/pages/Professional/subpages/QT/Tables/pbydrug.htm). Moreover, this antipsychotic provoked an inhibition of the I_{KI}, I_{sus}, I_{to} and I_{Na} currents in human atrial myocytes (www.fenichel.net/pages/Professional/subpages/QT/Tables/pbydrug.htm).

On isolated hearts of feline and guinea-pig haloperidol was infused at increasing concentrations and the ECG recordings showed a well-evident concentration-dependent QT prolongation (Drici et al 1998; Hamlin et al 2004).

Lande and collaborators (2001) carried out an in-vivo screening on wild-type mice and transgenic mice overexpressing a dominant-negative KvLQT1 isoform. Among various drugs tested, haloperidol was injected i.p. and the ECG recorded a dose-dependent lengthening of the sinus

period in transgenic mice. A recent study on anaesthetized guinea-pigs showed that haloperidol elicited a dose-dependent QT prolongation (Testai et al 2004).

On a halothane-anaesthetized dog model, the electrophysiological effects of haloperidol, and of other drugs, were evaluated. At clinical doses, haloperidol prolonged the monophasic action potential (MAP) duration and the effective refractory period (ERP), while at doses 10 times higher than the clinical doses it induced *torsade de pointes* (Sugiyama 2003).

Droperidol, in isolated guinea-pig hearts, increased the MAP duration concentration dependently and patch-clamp experiments performed on isolated guinea-pig ventricular myocytes confirmed the blocking action on the I_{Kr} current (Drolet et al 1999).

On Purkinje fibres droperidol caused EADs at doses between 0.3 and 3.0 μM, and had a behaviour similar to antiarrhythmics (Adamantidis et al 1994).

Antipsychotic benzodiazepines and analogues

The incidence of QT prolongation or *torsade de pointes* events in patients treated with these antipsychotics is very small. For example, sudden death cases of patients in therapy with clozapine were generally linked to myocarditis or cardiomyopathy (Grohmann et al 1989; Klimke & Klieser 1994; La Grenade et al 2001); nevertheless a retrospective analysis conducted by the Seoul National University Hospital Treatment-Resistent Schizophrenia Clinic showed ECG abnormalities in clozapine-treated subjects. Among 61 cases analysed, only two had a QT interval > 500 ms, and one had an abnormal ECG baseline (Kang et al 2000).

A study of the literature on olanzapine did not reveal a statistically significant incidence of QT interval prolongation; however, the maximum dose evaluated is usually 20 mg day^{-1} (Czekella et al 2001a, b). Recently, two cases of QT prolongation in olanzapine-treated women have been reported. In both cases the dosage of olanzapine was between 40 and 60 mg day^{-1} (Dineen et al 2003; Gurovich et al 2003).

The pre-marketing clinical trials for quetiapine do not describe any QT interval prolongation when the drug is administered at therapeutic doses, but in overdose conditions the QT interval was markedly prolonged (Harmon et al 1998; Nudelman et al 1998; Gajwani et al 2000; Physician's Desk Reference 2000a, b; Pollak & Zbuk 2000).

Two cases of prolonged QT interval were reported in patients ingesting an overdose of quetiapine, but life-threatening ventricular arrhythmias did not develop (Gajwani et al 2000; Physician's Desk Reference 2000a, b).

A case of QT interval prolongation with therapeutic doses of quetiapine was observed in a 46-year-old schizophrenic woman. She was treated with sertraline and quetiapine but lovastatin was also added to control the lipidic levels. Two months later, an ECG recording showed a QT prolongation; the reduction of lovastatin dosage gave a normal QT interval. It was hypothesized that lovastatin, by CYP450 inhibition, increased the plasmatic concentrations of the antipsychotic and, consequently, its toxicity (Frust et al 2002). Moreover, the case of a 50-year-old woman in therapy with quetiapine and several others drugs to cure schizoaffective disorder, obesity, obstructive sleep apnoea, hypercholesterolaemia, congestive heart failure, hypertension, asthma and chronic obstructive pulmonary disease has been reported. Admitted to the hospital, the patient showed a prolonged QT interval but, in this case, a relationship between the antipsychotic and QT prolongation could not be established because of the multiple pharmacological treatments (Gupta et al 2003).

Pre-clinical studies on HERG/CHO cells or on HERG/HEK cells showed the inhibitory effects on cardiac repolarization due to blocking of the Kr channels by these benzodiazepines (Kongsamut et al 2002; www.fenichel.net/pages/Professional/subpages/QT/Tables/pbydrug.htm).

Clozapine, olanzapine and other antipsychotics were also tested in isolated feline hearts. They were infused cumulatively and showed a concentration-dependent prolongation of the QT interval, but their potencies were lower than those of haloperidol and risperidone (Drici et al 1998).

Finally, in isolated rabbit ventricular cardiomyocytes, in isolated sheep Purkinje fibres and in guinea-pig papillary muscle the ability of quetiapine to reduce the I_{Kr} current was evaluated. This was of the same order of magnitude as those that inhibited the calcium and sodium currents. This pattern contrasts with the profile of other atypical antipsychotics, which reduce the HERG current at lower concentrations than sodium or calcium currents. Moreover, in isolated sheep Purkinje fibres and in guinea-pig papillary muscle quetiapine did not lengthen the action potential duration (APD) (Duffy et al 2001).

Benzamides

Data relating to the benzamides sulpiride and sultopride are relatively few. Sugiyama and colleagues (2002) report the case of an 81-year-old woman in week-long therapy with sulpiride (150 mg day^{-1}). She had a syncopal attack and the ECG recording revealed a prolonged QT interval, while the plasmatic concentrations of K^+ ions were in the normal range. After the interruption of sulpiride therapy her QT values become shorter. A causal link among sulpiride treatment, QT prolongation and syncope is suspected, but there is not sufficient evidence to show this (Sugiyama et al 2002). Nevertheless, later the authors encountered a second patient with a sulpiride-induced *torsade de pointes* episode (Takeda et al 2001).

In 2003, Su et al published a pilot study to evaluate the QT interval in antipsychotic-treated patients. The subjects were drug-free or sulpiride- and haloperidol-treated. They received sulpiride for 2 weeks, then haloperidol for 2 weeks. The authors found that the QT prolongation was associated with the use of sulpiride, but not with haloperidol (Su et al 2003).

For sultopride the first *torsade de pointes* case reported was a poisoning, and was preceded by a QT prolongation. The episode was resolved with potassium chloride and pacemaker stimulation (Montez et al 1992).

Another case of *torsade de pointes* considered a 48-year-old woman whose QT interval was 668 ms. This

went back to a normal value after the infusion of magnesium sulfate and the discontinuing of the sultopride treatment (Lande et al 1992).

The pre-clinical evaluation of the cardiotoxicity of sulpiride was assessed in two canine models: the first was represented by halothane-anaesthetized dogs, the second by chronic AV block dogs. Sulpiride induced QT prolongation in the canine halothane-anaesthetized model, while it induced *torsade de pointes* (following QT prolongation) in chronic AV block dogs. These results suggest that patients at risk of elevated plasmatic concentrations of the drug and/or having pre-existing susceptibility to QT prolongation should be monitored carefully (Sugiyama et al 2002).

The effects of sultopride were tested on isolated Purkinje fibres. It had a behaviour similar to some antiarrhythmic drugs, and the highest doses produced EADs (Adamantidis et al 1994). Moreover, the in-vivo screening of several antipsychotics (among them sultopride) by Lande and colleagues (2000) on transgenic for the KvLQT1 isoform and wild-type mice showed a lengthening of the sinus period in transgenic mice but not in wild-type mice.

Heterogeneous chemical classes

Other atypical antipsychotics may also cause cardiac abnormalities, as QT prolongation. In the UK between 1971 and 1995, 16 deaths and 24 other cases of life-threatening cardiac events in patients in therapy with pimozide were reported to the Medical Control Agency. This led to recommendations in the UK and USA to record periodical ECGs in patients treated with pimozide (Committee on Safety of Medications – Medical Control Agency 1995). Among the 24 cases reported, there is a case of a patient who developed *torsade de pointes* after the ingestion of 800 mg of pimozide as suicide attempt. An injection of lidocaine and magnesium resulted in the QT interval returning to normal values in 5 days (Krahenbuhl et al 1995).

Two fatal cases were described in patients receiving pimozide and clarithromycin; hence, in 1999, a study was performed in order to evaluate a possible link among clarithromycin effects, pimozide pharmacokinetics and QT changes. Twelve subjects (seven men and five women) were selected and divided into two groups: a control group (treated only with pimozide) and a treated group (treated with pimozide after 5 days of clarithromycin administration). Blood samples were collected before and after pimozide administration, and analysed by HPLC. Moreover, before each blood sample was taken the ECG was recorded, and a QT prolongation was shown in the first 20 h in both groups. However, the patients in the treated group showed a QT prolongation higher than those in the control group, suggesting that clarithromycin increases the plasmatic concentrations of the antipsychotic, thus increasing the cardiotoxic risk (Desta et al 1999).

In several systems expressing the HERG-K^+ channel (HEK 293, XO and CHO cells), pimozide demonstrated the ability to inhibit the I_{Kr} current and, with a lower potency, the I_{Ks} and I_{Kur} currents (Kang et al 2000; Finlayson et al 2001; Osypenko et al 2001; www.fenichel.net/pages/Professional/subpages/QT/Tables/pbydrug.htm).

The study of Drolet et al (2001) on isolated guinea-pig ventricular myocytes confirmed the pimozide-induced block of the HERG-K^+ channel.

On the cardiotoxicity of risperidone there is a single report of sudden death of a 34-year-old schizophrenic woman, who was also treated with amantadine. She had a seizure episode, her heart arrested twice, then she died, without *torsade de pointes* experience but with a prolonged QT interval (Ravin & Levenson 1997).

In fact, a relationship between plasmatic concentrations of risperidone and QT prolongation has been estimated by an in-vivo study. The drug concentrations, evaluated by HPLC, were 4.5-fold higher in tissues than in plasma, in particular in myocardium (Titier et al 2002).

The in-vitro experiments on HERG/HEK and HERG/CHO cells, and also on human atrial and ventricular myocytes, showed an inhibitory action of risperidone on I_{Kr} current (Adamantidis et al 1994; Kongsamut et al 2002; www.fenichel.net/pages/Professional/subpages/QT/Tables/pbydrug.htm).

Moreover, in isolated feline hearts risperidone, infused at increasing concentrations, produced a QT prolongation (Drici et al 1998). Another study showed the link between risperidone and prolongation of APD in rabbit Purkinje fibres and in ventricular myocardium (Gluais et al 2002).

Sertindole was introduced to the European market in 1997, but in 1998 it was voluntarily suspended because during the clinical trials programme there were 12 unexplained sudden deaths and 23 cases of syncope among the patients being treated (Food and Drug Administration 1996; Lewis et al 2000; Wilton et al 2001).

The association with QT prolongation has been well described by Fritze and Bandelow (1998). In fact, there are reports of QT prolongation and two cases of *torsade de pointes* (Fritze & Bandelow 1998; Mack et al 2002). Hence, after a re-evaluation of the existing data and of the new pre-clinical, clinical and epidemiological information, sertindole was re-introduced to the European market in 2002 (Toumi 2002).

The ability of sertindole to reduce the I_K currents (K_r, K_I, K_{sus}, K_{to}) was observed, in pre-clinical phases, on human atrial myocytes, HERG/CHO cells and HERG channels expressed in mammalian cell lines (Rampe et al 1998; Kongsamut et al 2002; www.fenichel.net/pages/Professional/subpages/QT/Tables/pbydrug.htm). Finally, this result was confirmed with studies on isolated tissues of feline and rabbit (Drici et al 1998; Eckardt et al 2002).

Recently, a report containing both in-vitro and in-vivo investigations was published. The currents flowing through HERG and SCN5A channels, transfected into CHO cells, were measured and a significant reduction in I_{HERG} current was observed for sertindole. The authors have extended the study on sertindole to dogs, using in-vitro and in-vivo models. In the in-vitro protocol, the ventricular myocytes were isolated and the I_{Kr} current showed a sertindole-induced concentration-dependent inhibition, while the transmembrane action potential was prolonged without the appearance of EADs or abnormal

automaticity. Finally, sertindole was injected i.v. in dogs with complete AV block, and the ECGs and the MAP were recorded. Cumulative doses of the antipsychotic were administered and the ECGs showed a prolongation of QT interval with the highest doses ($0.5–1.0 - 2.0\,mg\,kg^{-1}$). The MAP duration increased only with the highest doses. No *torsade de pointes* was observed at clinical doses, confirming the results of Eckardt et al (2002) (Thomsen et al 2003).

Thiapride is generally used for the treatment of agitation, aggressiveness, anxiety and sleep disorders in elderly patients (Steele et al 1993). The first report of *torsade de pointes* considered an elderly patient who was treated with thiapride and other neuroleptics (Wilt et al 1993; Hunt & Stern 1995; Sharma et al 1998). Another case report concerns a 76-year-old man in therapy with frusemide and ceftriaxone after hospitalization for bronchitis and mild congestive heart failure. On the third day thiapride was added to ease the agitation; then a QT interval prolongation was recorded by ECG, and a *torsade de pointes* episode was shown by Holter. After the interruption of the thiapride treatment, the QT interval returned to normal values (Iglesias et al 2000).

In pre-marketing trials ziprasidone has been minimally associated with the development of arrhythmias; in overdose conditions a moderate QT prolongation has been observed (Burton et al 2000). Three cases of ziprasidone overdose have been reported. The first was a 38-year-old psychotic woman whose ECG revealed a borderline intraventricular conduction delay (Teasdel & Jannet 1974). In the second case, only a moderate QT change was shown (House 2002). The third case of QT prolongation was associated with an intentional overdose of ziprasidone and bupropion, ingested by a 17-year-old man with a history of severe depression. At the emergency department the ECG recorded a prolonged QT interval, and several days of cardiac monitoring and treatment were necessary to achieve a return to normal conditions (Biswas et al 2003).

Recently, a 52-year-old woman, in treatment for a hypokalaemia condition, received a cocktail consisting of fluoxetine, lamotrigine, amitriptyline and clonazepam to bring her emotional relief. She received also ziprasidone, to control mood, and the arrhythmogenic effect was observed. About a month after the interruption of ziprasidone, in a confused and ataxic state, she discontinued the potassium chloride treatment and began to self-administer ziprasidone. ECG monitoring showed a markedly lengthened QT interval that returned to normal using an i.v. of potassium and magnesium. This report demonstrates that ziprasidone can prolong the QT interval in patients with abnormal electrolyte levels (Teich 2003).

Finally, the effect of ziprasidone is not influenced by the association with CYP3A4 inhibitors because its metabolism follows the aldehyde oxidase pathway (Food and Drug Administration 2000a, b).

A modest but unequivocable effect of ziprasidone on repolarization was observed in pre-clinical studies on HERG/HEK and HERG/CHO cells and on human atrial myocytes (Kongsamut et al 2002; www.fenichel.net/pages/Professional/subpages/QT/Tables/pbydrug.htm).

Although no clinical evidence of QT prolongation and/or *torsade de pointes* development has been reported to date, the neuroleptic drug fluspirilene should also be considered as a potential torsadogenic agent because it causes a significant reduction of potassium currents flowing through HERG channels expressed in *Xenopus* oocytes (Osypenko et al 2001; Shuba et al 2001). It is noteworthy that testosterone showed a protective role against the inhibition of the HERG channel by fluspirilene, haloperidol and pimozide, suggesting a further intriguing explanation for the higher incidence of *torsade de pointes* in females (Shuba et al 2001).

Conclusions

Irrespective of the different pharmacodynamic properties accounting for the therapeutic efficacy of the several classes of antipsychotics and of their heterogeneous structural features, in many cases they share significant cardiac electrophysiological effects (Thomas 1994), such as the tendency to prolong the QT interval and interfere with a physiological cardiac cycle. Although univocal issues indicating the precautionary rules addressed to the correct management of the risk involved in the clinical use of torsadogenic drugs do not exist, interesting approaches can be found in the international literature (for example Viskin et al 2003). Undoubtedly, the use of psychoactive drugs is often associated with cases of *torsade de pointes* and also with sudden deaths. In this review, we have tried to focus attention on experimental results concerning the possible negative influences exerted by the main classes of antipsychotics on the cardiac repolarization process, and to emphasize the most indicative clinical reports. Taken together, these data seem to indicate that a pharmacological antipsychotic treatment is per se a potential cardiac risk factor. In our opinion such a therapy requires a careful evaluation of the pharmacological/toxicological profiles of other drugs concomitantly administered, to avoid any pharmacodynamic or pharmacokinetic interaction, and (when possible) a frequent ECG monitoring of patients that is geared to an early identification of cardiac signals (such as QT prolongation), which are predictive of possible consequent serious anomalies, such as the development of *torsade de pointes* and life-threatening ventricular arrhythmias.

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