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Atypical Antipsychotics

From Potassium Channels to Torsade de Pointes and Sudden Death

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Contents

Abstract

Syncope and sudden death are features of schizophrenia that can be attributed to ischaemic heart disease, the use of antipsychotics (because of proarrhythmia or

other reasons such as pharyngeal dyskinesia) or the psychiatric disease itself. Cases have been described with most antipsychotics and have led to the withdrawal, temporary suspension from the market or restricted use of antipsychotics, such as sultopride, droperidol, sertindole or thioridazine.

Reviewing the available data shows that all antipsychotics tested affect the cardiac potassium channel, with the concentration that produces 50% inhibition (IC_{50}) ranging from 1 nmol/L (haloperidol) to 6 μmol/L (olanzapine). Experimental *in vitro* or *in vivo* electrophysiological studies have shown a dose-dependent increase in the duration of the action potential with various degrees of indicators of serious arrhythmogenicity. However, this does not always translate clinically into an increased duration of the QT interval or increased risk of torsade de pointes or sudden death in clinical trials or pharmacoepidemiological studies. In turn, QT prolongation in clinical trials does not always translate to an increased risk of torsade de pointes or sudden death.

The reasons for these apparent discrepancies are unclear and could be related to insufficiently powered field studies, low plasma and tissue drug concentrations with reference to *in vitro* data or drug effects on other receptors or ion channels that have a protective effect. Alternatively, risks that were not apparent from preclinical or clinical data could be related to the use of the drug in high-risk patients, metabolic interactions or other factors that would only be encountered in large postmarketing populations. The assessment of cardiovascular safety, both preclinical and during premarketing clinical trials, needs to be supported by appropriately powered pharmacoepidemiology studies.

The first reports that patients might be at increased risk of arrhythmia and sudden death because of antipsychotics appeared in the early 1960s, when thioridazine[1-3] was found to prolong the QT interval. Most published cases have involved phenothiazines[4-7] but almost all other antipsychotics[8-12] have also been involved, including newer drugs such as risperidone.[13,14] Sertindole was suspended voluntarily in the EU in 1998 following regulatory concerns over reports of serious cardiac dysrhythmia and sudden unexplained deaths. More generally, cases of sudden death and the occurrence of other electrocardiographic abnormalities have raised concerns about the safety of all antipsychotics. Further concerns are raised by data on mortality in schizophrenia, which is twice that in the general population.[15] This mortality, not fully accounted for by suicide or accidental death, may be attributable to drug-induced arrhythmias. Alternatively, sudden death was reported in patients with schizophrenia long before the first use of antipsychotics.[16]

The recent problems identified after the introduction of atypical antipsychotics has put the QT interval prolongation and risk of sudden death at the forefront of regulatory interest (International Conference on Harmonisation topic S 7B for preclinical assessment of their potential to prolong QT interval,[17] the recent US FDA conference [July 2003] and concept paper on clinical assessment of QT prolongation[18]). There have been several recent reviews of this rapidly evolving field[19-24] but none have really considered the problem across the spectrum from molecular pharmacology to epidemiology.

To date, whether and how antipsychotic drugs are involved in sudden deaths and other cardiovascular adverse effects has been incompletely investigated. The link between the purported primary abnormality, potassium channel inhibition and the final event, sudden death, is a complex one. It is modulated by a number of factors, such as effects on other ion channels or endogenous receptors, plasma and tissue

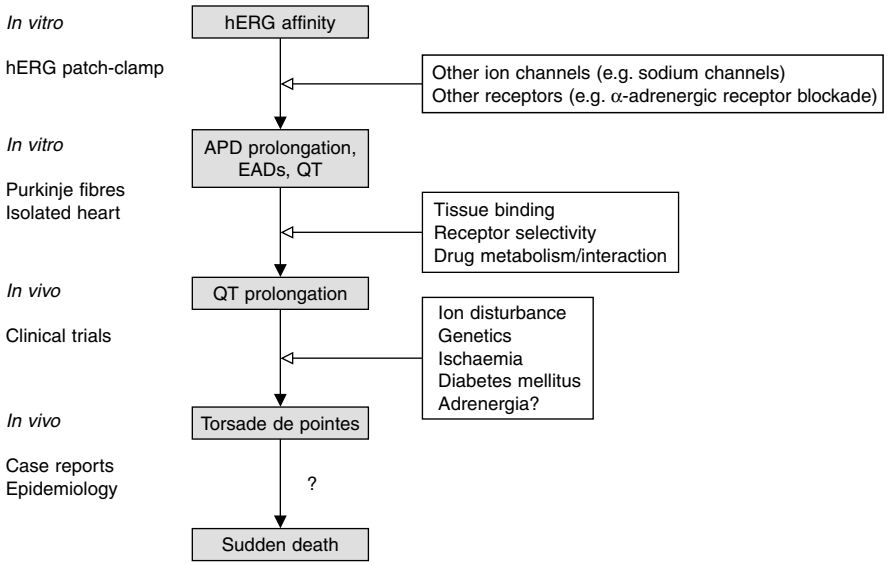

Fig. 1. From cardiac potassium channel to sudden death. **APD** = action potential duration; **EAD** = early after depolarisation; **hERG** = human ether-a-go-go related gene.

binding characteristics, drug metabolism and interactions, predisposing factors such as serum ion disturbances and genetic changes in cardiac repolarisation characteristics. Other arrhythmogenic disorders such as cardiac ischaemia or diabetes mellitus may coexist, or adrenergic factors, which make the link between human ether-a-go-go related gene (hERG) inhibition or QT prolongation and the risk of torsade de pointes or sudden death, less obvious than, for example, the relationship between cyclo-oxygenase (COX)-1 inhibition and the risk of gastric bleeding, or β_2-adrenergic receptor blockade and asthma.

Clinical QT prolongation with some atypical antipsychotics is observed in approximately 10% of users (0.1). Torsade de pointes or surrogates are reported with a frequency of about 1 in 10 000 (0.0001) users. Torsade de pointes is usually spontaneously self-terminating; the death rate is 1/10 of patients with torsade de pointes, i.e. 0.00001 of all patients taking the drug.[25] What is really needed is an understanding of how to predict, among the many patients with QT prolongation, the patients that will develop torsade de pointes or worse, will die. There are indications that in the general population, simple corrected QT (QTc) prolongation in the absence of cardiac risk factors is not indicative of an increased risk of sudden death.[26]

The aim of this review is to examine the relationship between atypical antipsychotics and sudden death. To assess such risks, we have conducted a review of available data concerning electrophysiology and potassium channels, experimental designs (action potential duration [APD], QT *in vitro*), ECG and QT prolongation, torsade de pointes and sudden death in general and, more specifically, with atypical antipsychotics (figure 1). Finally, we discuss how *in vitro* and *in vivo* preclinical models can be related to clinical findings and be used to evaluate the cardiac toxicity of these drugs.

This review is aimed at physicians and regulators in the field of drug safety and underlines the scarcity of epidemiological data that could help to bring preclinical and clinical data into focus.

1. From Potassium Channels to Torsade de Pointes

1.1 Electrophysiology of Cardiac Depolarisation and Repolarisation

The depolarisation of ventricular cells is the result of a rapid influx of sodium ions though selective sodium channels and its duration is measured by the QRS interval. The repolarisation involves calcium, sodium and several potassium channels. The human ventricular action potential consists of five sequential phases (figure 2).[27-29]

Phase 0: The upstroke of the action potential is primarily a consequence of a rapid, transient influx of Na^+ (sodium current [I_{Na}]) though Na^+ channels.

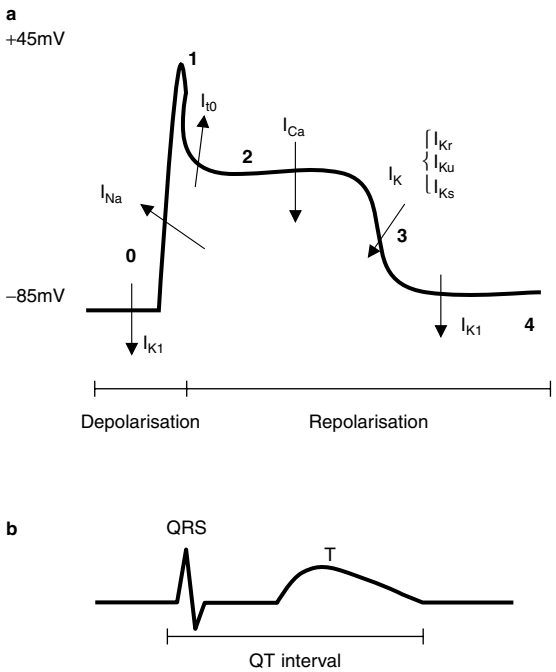

Fig. 2. The cardiac action potential: (**a**) action potential showing the five phases of cardiac depolarisation and repolarisation with ion current directions during activation of the different ion channels; (**b**) ECG. I_{Ca} = calcium current; I_K = potassium current; I_{K1} = inwardly rectifying potassium current; I_{Na} = depolarising sodium current; I_{t0} = transient outward potassium current; I_{Kr} = rapidly activating delayed rectifier potassium current; I_{Ks} = slowly activating delayed rectifier potassium current; I_{Ku} = ultra rapidly activating delayed rectifier potassium current.

Phase 1: The termination of the upstroke of the action potential and early after depolarisation (EAD) phase result from the inactivation of Na^+ channels and the transient efflux of K^+ (transient outward potassium current [I_{to}]) though K^+ channels.

Phase 2: The plateau of the action potential is a reflection of a balance between the influx of Ca^{2+} (calcium current [I_{Ca}]) though L-type Ca^{2+} channels and outward repolarising K^+ currents.

Phase 3: The sustained downward stroke of the action potential and the late repolarisation phase result from the efflux of K^+ (rapidly activating delayed rectifier potassium current [I_{Kr}] and slow activating delayed rectifier potassium current [I_{Ks}]) though delayed rectifier K^+ channels.

Phase 4: The resting potential is maintained by the inward rectifier K^+ current (I_{K1}).

The prolongation of the QT interval[27,29,30] in the ECG is caused by prolongation of the action potentials of ventricular myocytes, brought about by a reduction of outward currents and/or enhancement of inward currents during phase 2 and 3 of the action potential. A reduction in net outward current and/or an increase in inward current can potentially facilitate the development of EADs.[27,29,30] They occur preferentially in mid-myocardial cells and Purkinje cells. EADs are depolarisations occurring during phase 2 and 3 of the transmembrane potential before repolarisation is complete. Prolongation of the action potential allows reactivation of slow inward Na^+ and Ca^{2+} currents by reactivation of the L-type calcium current and/or activation of the sodium-calcium exchange current. EADs may give rise to one or more premature action potentials, interrupting early phase 3 repolarisation and possibly resulting in multifocal ventricular extrasystoles and torsade de pointes.

In the inherited form of the long QT syndrome, prolongation of the cardiac repolarisation phase has been shown to result from both potassium and sodium channel defects. Potassium channel genes known to be involved include *KVLQT1-IKs*, *hERG-IKr* and *KCNE1* and *KCNE2 (minK)-IKs* (encoding an auxiliary potassium channel subunit). The sodi-

um channel gene shown to affect the QT interval is the *SCN5A* gene encoding I_{Na}. Drugs may prolong the QT interval by exerting effects on any of these known channels. However, the best studied of these is the hERG-I_{Kr} channel. Virtually all drugs known to cause torsade de pointes block the rapidly activating component of this delayed rectifier potassium current.[27,29]

1.2 Experimental Designs

Heterologous expression systems[27,30] have been mainly used to study drug effects on the I_{Kr} channel, starting with the microinjection of ion channel RNA into *Xenopus Laevis* oocytes. Mammalian recombinant expression systems are increasingly used with human embryo kidney cells (HEK 293), mouse fibroblast (C cells) and Chinese hamster ovary (CHO) cells, all of which have relatively little endogenous voltage-gated ion channel activity. Ionic currents are measured with conventional two-electrode voltage clamp recordings. These patch-clamp studies allow for the measurement of the degree of hERG current blockade by the different drugs that are tested. At least four different concentrations encompassing a 100–1000-fold range should be tested to determine the IC_{50}, the concentration required to produce a 50% blockade of hERG.

Whereas the disaggregated hERG-expressing cell[27,30] is an ideal model for studying ion currents, its APD variability, even when paced at constant cycle length, reduces its utility for studying action potentials. It is here that isolated tissues[27,30] serve an important purpose for studying the effects on all ionic channels in combination. It is ideal for screening a large number of compounds. Hypokalaemia or bradycardia that facilitate I_{Kr} block can be easily reproduced by changing electrolyte concentrations or stimulation rates. The species more frequently used are dog, rabbit and guinea pig. For isolated tissue studies, canine mid-myocardium and Purkinje fibres appear to be the most susceptible to the effects of the I_{Kr} block. Endo- and epicardial muscle should be studied as well to ensure that the potential for dispersion is explored. Isolated tissue studies allow for the measurement of APD and EADs.[27,30]

For screening large numbers of compounds, the Langendorff-perfused guinea pig or rabbit heart[27,30,31] studied with electrogram or monophasic action-potential recording techniques gives consistent information on I_{Kr} blocking drugs when compared with other compounds. Isolated perfused heart allows for the measurement of the QT interval. Torsade de pointes can be induced in the isolated rabbit heart by reproducing conditions and circumstances that are clinically known to be associated with an increased propensity to develop torsade de pointes (i.e. hypokalaemia and bradycardia).

1.3 ECG and QT Interval

The QT interval[27-29] (time from the beginning of the QRS complex to the end of the T wave) of the ECG is a measure of the duration of the ventricular depolarisation and repolarisation (figure 1). The QT interval is the time between the onset of depolarisation of the ventricles and the end of repolarisation. Prolongation of the QT interval is a surrogate marker for the ability of a drug to cause torsade de pointes. In individual patients an absolute QT or QTc interval >500ms is regarded as indicating an increased risk of torsade de pointes. However, torsade de pointes can occur with lower QT/QTc values or changes.

QT measurement is complicated by a number of factors, both practical and physiological.[27,30,32] For example, determination of the precise end of the T-wave may be made difficult by the presence of a U-wave, which may interrupt and artificially extend the T-wave, and by the use of higher ECG paper speeds, which compromise the accuracy of QT measurement. Even where precise and accurate measurement of the QT interval is possible, electrophysiological variation complicates evaluation. QT interval varies according to ECG lead, gender (females have longer QT intervals) and time of day. Drug-induced changes appear to be affected by the phase of menstrual cycle.[27,30,32] More importantly, the QT interval also varies with the heart rate, becoming shorter as heart rate increases. Various correction factors have been suggested, with the most commonly used being Bazett's correction (QTc =

$QT/RR^{1/2}$). This formula has wide acceptability in the study of non-iatrogenic QT changes but has limitations when applied to drug induced changes. This is because the formula overcorrects the QT interval at high heart rates and undercorrects the QT interval at low heart rates. Drugs themselves may alter heart rate and so can erroneously be reported to change (or not to change) the QT interval. These difficulties need to be remembered when considering the reported effects of drugs on the QT interval; observations from clinical trials may be derived from markedly different methods of QT or QTc measurement. A more uniform approach to drug-related QT assessment has been strongly advocated, but there remains, for the time being, no consensus on exactly how the QT interval should be measured nor the most appropriate method of evaluating drug-induced changes.

Other measures have been proposed to supplement QTc measurement and allow better prediction of the risk of dysrhythmia. QTc dispersion[27,33] (the maximum difference in QTc values on 12-lead ECG) has been suggested, but recent studies have failed to find an association between QTc dispersion and dysrhythmia or mortality.[34]

1.4 Torsade de Pointes and Sudden Death

Torsade de pointes describes the ventricular arrhythmia that results in the progressive twisting of the QRS axis around an imaginary baseline associated with a prolonged QT interval in the last sinus beat preceding the onset of arrhythmia. Torsade de pointes is generally spontaneously reversible but can result in pre-syncope, syncope and sudden death (ventricular fibrillation). This is often speculated as being the cause of antipsychotic-induced death.[27-29,35]

Certain disorders may predispose the patient to the occurrence of torsade de pointes, such as long QT syndrome or hypokalaemia, which can be caused by a number of drugs (e.g. diuretics, corticosteroids), bradycardia, QT prolongation by drugs (e.g. antiarrhythmics) and diabetes (increases QT dispersion).[20,27,29,36] The possible presence of cardiovascular or metabolic conditions that might facilitate the emergence of proarrhythmic adverse effects should be considered. Renal, hepatic failure and slow metaboliser status can lead to the accumulation of harmful concentrations of these drugs. The risk of sudden death is increased by cardiac ischaemia, diabetes and age.

2. What of the Antipsychotics, Especially Atypical Ones?

2.1 Channel Patch Clamp Studies

The effects of antipsychotics on the potassium channel have been explored by different patch clamp studies. These result in IC_{50} values, reported in the literature, of 14 nmol/L for sertindole,[37] 1 nmol/L for haloperidol[38] and 1 μmol/L for risperidone.[39-41] These values were found in different studies and may not be directly comparable because of methodological variations.

Kongsamut et al.[42] compared hERG channel affinities for a series of antipsychotic drugs. All the antipsychotics tested reduced peak tailed current in a dose-dependent manner but with different potencies. Dose-response relationships generated from this protocol yielded IC_{50} values as follows: sertindole 2.7 nmol/L; pimozide 18 nmol/L; risperidone 167 nmol/L; ziprasidone 169 nmol/L; thioridazine 191 nmol/L; quetiapine 5765 nmol/L and olanzapine 6013 nmol/L (table I).

2.2 Electrophysiology

Two major comparative electrophysiological studies of antipsychotics have been published: one study by Adamantidis et al.[43] on Purkinje fibres and another by Drici et al.[36] on isolated feline heart.

The data reported by Adamantidis et al.[43] show a concentration-dependent increase of the APD induced by droperidol. The APD was lengthened for concentrations from 1 μmol/L to 3 μmol/L and decreased for concentrations from 10 μmol/L to 30 μmol/L. For haloperidol and risperidone, the APD increased rapidly for concentrations >0.1 μmol/L. The effect on the APD was less marked for clozapine. In another report,[40] the authors investi-

Table I. Review of *in vitro* and *in vivo* data relating to electrophysical and clinical effects of antipsychotic drugs

Drug	*In vitro*[a]			*In vivo*[b]		
	IC_{50} (nmol/L)[42]	APD 90ms (3 μmol/L)[43]	rate of increased QTc (%)[36]	rate of increased QTc (%)[44]	no. of published case reports	
					QT prolongation, arrhythmia	torsade de pointes, sudden death
Haloperidol	1[38]	400	26	7.3	4[45-48]	12[8-10,47,49-57]
Sertindole	2.7	350	8.9	3	0	0
Risperidone	167	425	19	NS	2[35,58]/4 (overdose)[13,59-61]	1[14]
Ziprasidone	169	NS	NS	1.4	0	0
Quetiapine	5765	NS	NS	4.8	4[62-65]	0
Olanzapine	6013	325	NS	1.1	0	0
Clozapine	NS	325	NS	NS	2[66,67]	1[68]

a Patch-clamp, isolated heart and Purkinje fibres studies.

b Clinical trials and published case reports.

APD = action potential duration; **hERG** = human ether-a-go-go related gene; **IC_{50}** = concentration that produces 50% inhibition of hERG; **NS** = not stated; **QTc** = corrected QT interval.

gated the effect of risperidone on potentials recorded on Purkinje fibres and ventricular myocardium and potassium currents recorded from atrial and ventricular rabbit isolated myocytes. The results showed that risperidone (0.1–3 μmol/L) exerted potent lengthening effects on the APD in both tissues, with higher potency in Purkinje fibres, and caused the development of EADs at low stimulation rate. Risperidone (0.03–0.3 μmol/L) significantly reduced the current density of the delayed rectifier current and at 30 μmol/L decreased the transient outward and the inward rectifier currents.

The study by Drici et al.[36] was designed to test the potency of five antipsychotics (risperidone, olanzapine, sertindole, clozapine and haloperidol) in lengthening the QT interval of the perfused isolated heart. The hearts were infused with increasing concentrations of drugs (0.1–20 μmol/L) for 40 minutes intervals at each concentration. Data indicated that all tested drugs prolonged the QT interval in a concentration-dependent manner. Haloperidol and risperidone were significantly more potent than sertindole, clozapine or olanzapine. At a concentration of 0.5 μmol/L, haloperidol lengthened the interval by 26.2 ± 0.7%, risperidone by 19.4 ± 2.2% and sertindole by 8.9 ± 3.5%.

Production of EADs may not be linearly related to QT prolongation, though most of the drugs tested by Adamantidis et al.[43] also induced EADs at low pacing frequencies. Despite similar QT prolongation, no torsade de pointes or EADs were generated with sertindole, in contrast with sotalol.[69] Other studies looking at individual products such as sertindole[69] or sulpiride[70] have confirmed the results of the comparative studies cited previously.

2.3 QT Lengthening in Patients

2.3.1 QT Lengthening Studies in Schizophrenic Populations

Many studies have compared the QTc interval in patients treated with antipsychotics with control patients. These studies show a lengthening of the QTc interval with most antipsychotics.[33,35,71] In the study by Reilly et al.,[35] an abnormal QTc was present in 8% of 495 psychiatric patients. This study

showed that antipsychotic drugs cause QTc lengthening in a dose-related manner and that the effects are substantially higher for thioridazine or droperidol than for other antipsychotics. These drugs may therefore confer an increased risk of drug-induced arrhythmia.

Cardiovascular mortality has also been studied from data collected in a large North American study of nearly 100 000 outpatients with schizophrenia who were treated with antipsychotics.[44] This study originated from unpublished preclinical work comparing ziprasidone with other antipsychotics. QTc data were corrected using Fredericia's formula ($QT/RR^{1/3}$), which is better adapted to drugs that tend to increase heart rate than Bazett's formula ($QT/RR^{1/2}$). The mean increases in QTc were 1.1% for olanzapine, 3% for risperidone, 4.8% for quetiapine, 7.3% for haloperidol, 15.4% for ziprasidone and 29.6% for thioridazine.

Though there was a dose-dependent QT prolongation in the schizophrenic population, there was no direct evidence that linked the extent of drug-induced QTc lengthening with the risk of torsade de pointes or sudden death.

2.3.2 Clinical Cases of QT Lengthening

Death and torsade de pointes have been described with most or all classical antipsychotics, especially thioridazine. However, we focused on atypical antipsychotics since these agents are being increasingly used in clinical practice because of their superior general tolerability and, possibly, efficacy.

Clozapine

A retrospective study[66] of 61 patients treated with clozapine reported a dose-dependent lengthening of the QT interval. Although a substantial proportion of patients developed ECG abnormalities, most of the abnormalities were benign and did not hinder further treatment. Another study[67] with 21 patients treated with clozapine reported a mean QTc interval of 521ms. In one case, the QTc interval reached 624ms. In the clozapine database of 2.8 million patients spanning 27 years, apparently only three unconfounded cases of QT prolongation were found.[68]

Olanzapine

To date, no case of QT prolongation or arrhythmia in patients treated with olanzapine has been described. Some studies[72,73] showed that olanzapine at therapeutic doses did not contribute to QTc prolongation.

Quetiapine

A case of prolongation of the QTc interval with co-administration of quetiapine and lovastatin has been described.[62] The authors suggested that lovastatin caused an increase in plasma quetiapine concentrations through competitive inhibition of cytochrome P450 3A4. To date, three other reports of quetiapine overdose have shown QT interval prolongation,[63-65] though there have been additional cases reported to the regulatory authorities.[74]

Risperidone

Shortly after the introduction of risperidone in clinical practice, cases of QT interval lengthening were reported in patients with electrolyte disorders such as hypokalaemia. Several cases of widening QRS complex and lengthening of the QTc interval were reported with risperidone at therapeutic doses[35,58] and in cases of overdose.[13,59-61]

Sertindole

A prolongation of the QT interval was observed with sertindole in early clinical trials, with a mean QTc interval prolongation of 19.7ms. None of the patients developed clinical or electrocardiographic evidence of cardiac dysrhythmia during sertindole treatment or other clinical evidences of cardiac abnormalities.[75]

Ziprasidone

Ziprasidone has been reported to cause an average QTc prolongation of approximately 20ms.[76] The manufacturer reported only two cases with a measured QTc interval of >500ms. To date, no cases of QT prolongation or arrhythmia in patients treated with ziprasidone have been described.[28] Only one case of overdose has been described[77] but with no electrocardiographic abnormalities.

A recent publication refers to the results of a randomised clinical trial of six antipsychotics with or without metabolic inhibition.[78] This study com-

pared haloperidol, thioridazine, ziprasidone, quetiapine, olanzapine and risperidone in patients with schizophrenia. The mean QTc interval increase was greatest with thioridazine but was present for all drugs studied. The QTc interval was not modified by metabolic inhibitors, and in no case did it exceed 500ms.[78] However, the patient populations were relatively small, 20–30 per group, so the significance of the latter finding is rather doubtful.

Aripiprazole

Aripiprazole was recently recommended for marketing approval in Europe. Clinical trials do not indicate QTc lengthening and possibly even indicate QTc shortening.[79-82] However, there is little clinical experience with this drug at this time.

2.4 Torsade de Pointes and Sudden Death

2.4.1 Studies on Death in Schizophrenic Populations

Some studies[83,84] have shown a high risk for premature deaths, from both natural and unnatural causes, in the schizophrenic population. In these studies, mortality in patients with schizophrenia was found to be approximately twice that of the general population. The excess mortality was partly a result of the high incidence of suicide. Nevertheless, 60% of the excess mortality was attributable to apparently natural causes of death: diseases of the circulatory, digestive, endocrine, nervous and respiratory systems and undetermined death.[83,84]

The occurrence of sudden unexplained death in mentally ill patients has been described since 1849, which is long before the advent of the first antipsychotics.[16] This is attributed to hyper-adrenergic stimulation during agitation. Another cause of death could be sudden hypotension related to the α-adrenergic receptor blocking properties of these drugs. Other causes of these deaths are coronary heart disease (risk is increased by sedentary lifestyles, obesity and smoking, which are frequent in these patients), post-ictal death, food inhalation leading to asphyxiation and heat stroke.[15,83]

In a retrospective analysis of a population of 3623 patients with schizophrenia, investigators found the life expectancy to be as much as 20% shorter than that of the general population.[85] 301 patients died within a 10-year span, with cardiovascular deaths accounting for 20% of the mortality (61 patients). Among these patients, 15 did not have diagnoses of either ischaemic heart diseases (accounting for 36 of the 61 deaths) or cerebrovascular diseases (10 of the 61 deaths). It is possible that sudden death was involved in at least some of the 15 deaths, representing up to 5% of the total mortality.

Few data are available in the literature regarding the relationship between sudden unexplained deaths and antipsychotics. Mehtonen et al.[4] examined all medicolegal autopsies in Finland over a 3-year period. Among 24 158 patients, they found 49 sudden unexplained deaths among apparently healthy adults taking psychotropic medications. 46 of the 49 deaths occurred during treatment with a phenothiazine (primarily thioridazine – 28 of 46). Haloperidol and thioridazine were used at the same frequency but haloperidol represented 6 of the 46 deaths. Kumar[6] has also reported the role of phenothiazines in sudden deaths.

Montout et al.[15] looked for an association between the number and nature of antipsychotics and mortality in a prospective cohort of patients with schizophrenia. They confirmed that suicide was the first cause of death (54.3% of all deaths in the first year of follow-up). The cardiovascular deaths represented a small proportion (11% of all deaths in the first 3 years of follow-up). The study found an increased risk of global mortality in users of thioxanthenes, which was related to an increased risk of suicide. In this study, deaths from causes other than suicide or cardiovascular events occurred more frequently in patients treated by atypical antipsychotics. There were no differences between antipsychotics classes for cardiovascular deaths.

Using US Medicaid administrative data, Hennessy et al.[86] examined the rate of cardiac arrest and ventricular arrhythmia in patients with treated schizophrenia (haloperidol, thioridazine, risperidone or clozapine) and in non-schizophrenic controls (patients with glaucoma and psoriasis; both these conditions requiring long-term medication and neither

being associated with increased cardiac risk). Patients with treated schizophrenia had higher rates of cardiac arrest and ventricular arrhythmia than controls, with risk ratios ranging from 1.7 to 3.2. A dose-response relationship could be identified only for thioridazine; the dose ratio between the highest and the lowest dose was 2.5. Overall, the risk with thioridazine was no higher than with haloperidol. Risperidone was the only drug that had higher rate ratios than haloperidol for cardiac arrest and ventricular arrhythmia and for death. The rate ratio for cardiac arrest and ventricular arrhythmia for risperidone compared with haloperidol was 1.5.

A recent case-control study of psychiatric inpatients dying suddenly in five hospitals in North East England and surviving matched controls was used to identify risk factors.[87] Odds ratios were computed. 69 case-control clusters were identified. Probable sudden death was significantly associated with hypertension, ischaemic heart disease and current treatment with thioridazine. Other individual antipsychotic drugs were not associated in this way. The authors concluded that the likely mechanism was drug-induced arrhythmia.

The conclusion is that most sudden deaths in psychiatric patients occur in those treated with antipsychotics, but the assessment of causality is difficult. There are indications that antipsychotics, especially thioridazine, can alter the ECG and may possibly be associated with a higher risk of sudden death. However, more epidemiological data are needed to confirm this risk in the absolute and for individual drug classes.

2.4.2 Establishing an Antipsychotic Drug as the Cause of Sudden Death

As mentioned previously, assessing the causal link between the administration of an antipsychotic drug and a sudden unexpected death has proved to be difficult in practice. As the Hennessy et al.[86] study showed, thioridazine may present an enhanced risk of cardiac arrest or ventricular arrhythmia but probably only at dosages of >600 mg/day. This, together with some c ase-reports and clinical impressions, would suggest that there is a verifiable relationship between high doses of antipsychotic medication and sudden death. Post-mortem reports, particularly when incorporating plasma drug concentrations obtained from the cadaver, should be of crucial importance. However, there are complications.

First, what is meant by 'sudden death'? Jusic and Lader[88] proposed that "sudden, unexpected, unexplained death can be defined as death within 1 hour of symptoms (excluding suicide, homicide and accident), which was both unexpected in relation to the degree of disability before death and unexplained because clinical investigation and autopsy failed to identify any plausible cause".

Second, the dosage and even the identity of the antipsychotic drug being taken may be unestablished. Patients with schizophrenia or severe psychosis are notoriously poor at adhering to their prescribed regimens. The mere existence of a prescription that has been filled by a pharmacy may be irrelevant if the patient has stopped taking the medication, obtained other medications or is abusing 'street drugs'.

Third, the rate of suicide among schizophrenic patients is high, particularly in the earlier stages of the disorder. Consequently, sudden unexpected death may follow the ingestion of an overdose rather than arise in the course of therapeutic medication.

Fourth, the validity of post-mortem drug concentrations taken after death is open to question. Because of the complexity of post-mortem redistribution, and considering the scarcity of data concerning post-mortem drug evolution of plasma concentrations,[88,89] post-mortem plasma concentrations are not generally very helpful to determine plasma concentration at the time of the death.

2.4.3 Clinical Cases of Torsade de Pointes and Sudden Death

Clozapine

Only one case of sudden death in patients receiving combination therapy with clozapine and sertraline has been described.[90] The most likely cause of death was sudden cardiac death due to acute cardiac arrhythmia.

Some reports[91,92] have shown that clozapine therapy may be associated with potentially fatal

myocarditis and cardiomyopathy in physically healthy young adults with schizophrenia. In 8000 patients treated with clozapine, 15 cases of myocarditis and 8 cases of cardiomyopathy were identified.[91] All cases of myocarditis (five deaths) occurred within 3 weeks of starting clozapine. Cardiomyopathy (one death) was diagnosed up to 36 months after clozapine therapy was started. Necropsy results showed mainly eosinophilic infiltrates with myocytolysis consistent with an acute drug reaction. Coulter et al.[92] have shown that there is an association between myocarditis or cardiomyopathy and lithium, chlorpromazine, fluphenazine, haloperidol and risperidone. Myocarditis may increase the risk of arrhythmia but is peripheral to the issue addressed in this review.

Risperidone

Only one case of death following cardiac arrest has been described, with a lengthening of the QT interval at 480ms and possibly related to a QRS widening at 160ms[14] after administration of a therapeutic dose of risperidone and in the absence of cardiovascular history.

Sertindole

Although sertindole was suspended because of reports of suspected sudden death to the UK authorities, to date there has been no published report of sudden death, arrhythmia or myocarditis associated with this agent. Wilton et al.[93] compared mortality rates in a sertindole cohort to those in a comparator cohort treated with risperidone and olanzapine and found no difference between the groups, albeit with wide CIs in the sertindole cohort because of its small size. Further analysis of postmarketing epidemiological data found no confirmatory evidence of excess mortality risk with sertindole and the drug was reintroduced to the market in 2002.[74]

Other Atypical Antipsychotics

No case report has been published to date of either sudden death or severe dysrhythmia with olanzapine, ziprasidone or quetiapine. However, olanzapine is associated with increased weight and diabetes mellitus and is also a risk factor for sudden death; the others have only been recently introduced to the market.

3. Discussion

The data presented in this review indicate that not all antipsychotic drugs that inhibit potassium channels at the cellular level are associated equally with prolongation of the QT interval in patients, and the potential for QT prolongation is not always equally correlated with torsade de pointes and sudden death (table I). hERG channel inhibition is commonly used as a screening method to predict the ability of antipsychotics and other drugs to prolong the QT interval. However, the exact relationship between hERG channel blockade, target receptor binding affinity and clinical QT prolongation is not known, especially the relevance of *in vitro* results to *in vivo* tissue concentrations. How can *in vitro* and *in vivo* preclinical models be related to clinical findings and be used to approach the cardiac toxicity of these drugs? (figure 1).

3.1 Relationship Between Potassium Channels and Electrophysiology

There is no clear relationship between the I_{Kr} block and the development of torsade de pointes.[30,94] The multiple pharmacological effects of a drug can modulate the extent to which it prolongs repolarisation. Effects on other channels, some opposing and some enhancing the effect on I_{Kr}, may also coexist. Because drugs that block I_{Kr} may also act on other ion channels, with complex consequences, hERG inhibition may not be fully predictive of clinical risk.

For instance, from a patch-clamp study,[40] the concentrations required to produce a 50% block of hERG were in the nanomolar range for sertindole and haloperidol and micromolar for risperidone. However, haloperidol and risperidone induced drastic prolonging effects on the APD,[43] but sertindole had only a minimal effect. Similar differences in the intensity for prolonging the QT interval (haloperidol > risperidone > sertindole) were found in isolated perfused feline heart.[36] Despite comparable QT prolongation in rabbit heart, sertindole did not

display the proarrhythmic profile typical of other blockers of I_{Kr} such as sotalol.[69]

The differences may be partly explained by different modes of interaction with the potassium channel and the concomitant depression of other action potential parameters, especially the maximal rate of rise of phase 0 action potential amplitude and plateau duration with sertindole that indicates Ca^{2+} and Na^{+} current reduction, which makes the prolonging effects of QT prolongation less likely to occur,[40] or additional pharmacological properties such as the ability to inhibit I_{Na} and/or to block α_1-receptors. In addition, the *in vivo* effects of certain antipsychotics on plasma adrenaline (epinephrine), noradrenaline (norepinephrine) or serotonin levels may further complicate the application of *in vitro* studies to *in vivo* risk.

3.2 Relationship Between Electrophysiology and QT Lengthening

A number of questions regarding the interpretation of data obtained from electrophysiology remain unanswered. What degree of selectivity between the target receptor and hERG should be considered acceptable? How does electrophysiology *in vitro* relate to QT prolongation in clinical studies?

3.2.1 Pharmacodynamic Settings: Comparison Between Human Ether-a-go-go Related Gene (hERG), Dopamine D_2 and Serotonin 5-HT_{2A} Receptor Affinities

Kongsamut et al.[42] compared the affinity of antipsychotics to human dopamine D_2 and serotonin 5-HT_{2A} receptors with that of hERG, since it is generally believed that the antipsychotic compounds derive their therapeutic efficacy from binding to one or more of these receptors.[95] From these data, pimozide, thioridazine and sertindole display little (<10-fold) or no selectivity for these receptors compared with their affinity for hERG. It is therefore not surprising that these drugs are associated with QT prolongation. Thus, pimozide prolongs the QT interval at therapeutic doses and may be associated with the development of torsade de pointes.[96] Likewise, thioridazine and sertindole are also associated with significant QT prolongation in clinical use.[28,29,97] On the other hand, risperidone and olanzapine display the greatest degree of selectivity when the affinities of both D_2 and 5-HT_{2A} receptors were compared to that of hERG. Based upon *in vitro* criteria alone, it would be expected that olanzapine would have the least potential to produce QT prolongation in clinical settings, which is concordant with QTc values obtained from the US FDA study.[44]

However, it has been shown that some antipsychotics could also block the cerebral potassium channels, which may contribute to the antipsychotic effect.[98]

3.2.2 Pharmacokinetic Settings: Comparison Between hERG Affinity, Plasma Drug Concentrations and Drug Distribution

Kongsamut et al.[42] showed that the examination of total plasma drug concentrations relative to hERG channel affinities also seems useful for predicting the potential of a drug to increase QT interval duration, at least for the highly protein-bound antipsychotic drugs. The ratio of total plasma concentration to hERG IC_{50} appeared to correspond well with the observed changes in QTc.[44]

Another problem with hERG channel testing and APD measurement is that these approaches fail to account for the possible differences in concentrations between the heart and the brain caused by drug distribution characteristics. Also, how *in vitro* concentrations used for electrophysiology relate to actual *in vivo* tissue concentrations remains unknown. In this context, the study of myocardial distribution of antipsychotics would be helpful. The tissue binding of risperidone and olanzapine has been studied in the rat brain, lung, kidney and liver.[99,100] The ratio between myocardial tissue and plasma concentrations in guinea pig for risperidone[101] was approximately 4.5, which was higher than that reported by Aravagiri et al.[100] to the brain (brain to plasma ratio: 0.22). The ratio for haloperidol was 7.[102] This could explain the more important QTc prolongation with haloperidol than with risperidone that has been observed in patients. These results can be related to differential drug lipophilicity. The lower binding of risperidone and its lower effect on QT duration may

be explained by its lower lipophilicity as expressed in the partition coefficient (P) between n-octanol and aqueous buffer solution at pH 10: log P for risperidone is 3.04, whereas log P for haloperidol is 3.36.[100]

Consequently, myocardial binding studies are a complementary approach to account for the relative cardiac toxicity of antipsychotics.[102] These data underscore the importance of interpretation of *in vitro* electrophysiological data in the context of other pharmacodynamic (other cardiac ion channels, target receptor affinity) and pharmacokinetic (total plasma drug concentration and drug distribution to the brain and myocardium) parameters.

3.3 Relationship Between QT Lengthening and Torsade de Pointes

From QT studies, it seems that QTc interval lengthening may be a predictor of sudden death in patients, and the extent of drug-induced QTc interval lengthening is thought to be an important marker of arrhythmia risk by drug regulatory authorities. However, it can not always be assumed that the greater the prolongation of the QTc interval, the greater the risk of dysrhythmia or sudden death in all patients.[26] One reason for this is the confounding effect of heart rate changes induced by some drugs (for instance, because of an α-receptor blocking effect) that will affect the measure of QTc according to the correction method used. Another reason is that the heart rate itself affects the risk of torsade de pointes; yet another reason is that clear exceptions to this trend exist, the most notable of which is amiodarone, which prolongs QTc considerably but is rarely associated with torsade de pointes or sudden cardiac death. As described before, the risk of torsade de pointes is increased by different factors such as long QTc interval, hypokalaemia, diabetes or cardiac ischaemia, which are frequently experienced by the schizophrenic population.[20,27,29,36]

Clinical data do not support any clear difference between antipsychotics in the nature of the arrhythmic risk or its frequency, in terms of torsade de pointes or sudden death, despite clear differences between the drugs for QT prolongation in clinical trials. The only exception to this assertion concerns thioridazine, which is associated both with the largest QT prolongation at therapeutic doses[44] and with a clearly increased risk of torsade de pointes or sudden death in epidemiological studies.[4,6,86] There does not seem to be such clear-cut excess risks with those atypical antipsychotics that prolong the QT interval the most (e.g. ziprasidone, sertindole). However, there is a dearth of good large-scale epidemiological studies of the newer atypical antipsychotics that could assess their individual risks for cardiovascular deaths, in balance with other more frequent causes of death such as suicide. However, despite the high mortality rate in patients with schizophrenia, sudden death and, particularly, torsade de pointes remain very rare events, so that such epidemiological studies or large clinical trials would need to include several thousand patients to have enough power.

3.4 Clinical Implications

The relationship between some antipsychotic drugs, particularly in high or supratherapeutic doses and adverse cardiac events, including sudden death, is generally accepted, although many questions are unanswered.[103] Guidelines for the use of high-dose medication have been available for some time (e.g. Thompson[104]). Nevertheless, the relative risks among antipsychotic drugs, typical and atypical, remain unestablished or, at best, imprecise. Despite this imprecision of the relative risk of drugs, the prescriber must assume that antipsychotics in general present a degree of cardiac risk, even though for some drugs this risk may seem remote.[32] The prudent clinician will, therefore, adopt practical measures to minimise this risk as follows.

All psychotic patients, or if they are inaccessible, their caregivers or relatives, should be questioned about family history of heart disease, particularly of sudden premature death, to look for familial long-QT syndromes. Previous heart disease in the patient should be elicited and documented.[26] If possible, and if high doses are likely to be needed, plasma electrolyte estimations should be used to exclude abnormalities that might predispose to cardiac ar-

rhythmias. Polypharmacy with drugs known to prolong the QT interval should be avoided as should the use of drugs known to inhibit relevant cytochrome isoenzymes, even though recent data may be thought to be reassuring in this respect.[78] Combinations of antipsychotic drugs should also be avoided wherever possible, as therapeutic benefits of such associations are unestablished whereas drug interactions may be a hazard for the patient.[105] The use of depot antipsychotics should be carefully considered in view of their prolonged duration of action and inevitable prolonged toxicity if poorly tolerated.

High-risk patients include those with a personal or family history of QT prolongation; those with pre-existing heart disease or cardiac symptoms; patients in whom polypharmacy is unavoidable; those predicted to require high doses, as their illness becomes treatment-resistant over time; those with unreliable treatment adherence; and those abusing other drugs, licit or illicit.[106] In all of these, ECG monitoring should be instituted, whatever the drug used, and monitored throughout. Access to an expert cardiological opinion should be secured. Any definite prolongation of the QT interval or any cardiac dysrhythmia should lead to an immediate reduction of dose or cessation of the antipsychotic drug and to rapid expert review.

4. Conclusion

Antipsychotics inhibit the potassium channel, prolong APD and the QT interval and are associated with a risk of torsade de pointes, ventricular tachycardia, syncope and sudden death. Most published cases have involved phenothiazines, especially thioridazine, but other antipsychotics including atypical ones have also been involved. Although this effect has been known for a long time, the degree of risk associated with the various antipsychotics is still poorly known and few epidemiological data are available. Different *in vitro* approaches to account for the relative cardiac toxicity of antipsychotics have been reported but a number of questions regarding the interpretation of data obtained from these screens remain, including the relevance of *in vitro* concentrations to actual *in vivo* tissue concentrations. Further research is needed to predict the potential of a drug to increase the QT interval duration and to quantify the risk of sudden death. This underscores the importance of clinical data and postmarketing pharmacoepidemiological studies to further the understanding of the link between the electrophysiological changes and the actual clinical risk, in order to help decision makers, be they prescribers or regulatory authorities.

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