QTc interval prolongation and antipsychotic drug treatments: focus on sertindole

Eva Lindström1, Lars Farde2, Jonas Eberhard3 and Wilhelm Haverkamp1

1 Department of Psychiatry, Uppsala University, Sweden
2 Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden
3 Department of Clinical Science, Lund University, Sweden
4 Department of Cardiology, Charité University Hospital, Campus Virchow Clinic, Berlin, Germany

Abstract

Since the 1960s, physicians have been aware of electrocardiographic (ECG) abnormalities and cases of sudden death associated with the use of antipsychotic drugs in patients with schizophrenia. Explanations for such deaths have traditionally focused on drug-induced prolongation of the QT interval leading to the development of life-threatening ventricular arrhythmias such as torsade de pointes (TdP). It is now apparent that most conventional and atypical antipsychotics can cause dose-related prolongation of the corrected QT interval (QTc), although there are important differences in the potency of individual agents. This review discusses potential mechanisms underlying QTc prolongation and arrhythmogenesis and examines the evidence for a relationship between antipsychotic drugs and prolongation of the QTc interval. New electrophysiological and epidemiological data are presented which suggest there may not be a clear-cut cause–effect relationship between QTc prolongation and the development of ventricular tachyarrhythmias for all atypical antipsychotics. For at least one of these agents (sertindole), counter-balancing mechanisms may act to reduce the risk of proarrhythmic activity arising as a result of QTc prolongation.

Introduction

Available evidence indicates that schizophrenia is associated with a significant increase in mortality from both natural and unnatural causes (Brown, 1997; Brown et al., 2000; Tsuang and Woolson, 1978). For example, in a Finnish study all patients discharged from psychiatric hospitals during the year 1988 were followed up until 1992, and the standardized mortality ratio (SMR) was almost four times higher than in the general population (Sohlman and Lehtinen, 1999). The major causes of natural death were acute myocardial infarction and unspecified pneumonia. More recently, a meta-analysis of several studies looking at patients with schizophrenia showed that the all-cause death risk was 1.6 times higher, the mortality risk from unnatural causes was 4.3 times higher and the risk for suicide was nine times higher than expected (Harris and Barraclough, 1997). With respect to natural deaths, deaths from infectious diseases, endocrine, mental, circulatory, respiratory and genito-urinary system disorders all had significantly raised SMRs.

In addition to the increased mortality associated with schizophrenia per se, physicians have been aware since the 1960s of electrocardiographic (ECG) abnormalities and cases of sudden death in patients with schizophrenia who were receiving antipsychotics (Fowler et al., 1976; Hennessy et al., 2002; Hollister and Koesk, 1965; Leestma and Koenig, 1968; Mehtonen et al., 1991; Ray et al., 2001; Reilly et al., 2002). One possible explanation why antipsychotics could cause sudden death involves prolongation of the QT interval (Glassman and Bigger, 2001; Haddad and Anderson, 2002), which is the ECG correlate of prolongation of the cardiac action potential. In extreme cases, or susceptible individuals, prolongation of the QT interval increases the likelihood of developing life-threatening ventricular arrhythmias such as torsade de pointes (TdP) (Haverkamp et al., 2000). TdP is a rare but serious paroxysmal ventricular arrhythmia that can progress to ventricular fibrillation and sudden death.

It is now apparent that not only antipsychotics, but a wide range of drugs can prolong the QT interval, and
a significant number of these drugs have also been associated with the development of TdP (Haverkamp et al., 2000; Redfern et al., 2003). In recent years, concern about the risks of TdP and sudden death has led to withdrawal of some antipsychotic drugs from the market (e.g. droperidol) and the introduction of restricted prescribing guidelines (e.g. thioridazine, pimozide) or reductions in recommended maximum daily doses (e.g. haloperidol in the UK). Similar concerns have also delayed marketing approval for novel antipsychotics such as ziprasidone.

Sertindole is a new atypical antipsychotic drug, which was registered in the UK and several European countries in 1996 for the treatment of schizophrenia, but due to regulatory uncertainty with respect to the drug’s safety profile, its marketing authorization was suspended in 1998. In fact, the case of sertindole attracted real attention and initiated the present general focus on drugs having QT-interval-prolonging properties. The withdrawal of sertindole was followed by a series of studies on epidemiology as well as underlying mechanisms, and after submission of extended documentation, the European Committee for Proprietary Medicinal Products (CPMP) lifted its suspension on sertindole in 2002. Following its reintroduction, patients prescribed sertindole were all included in a large sertindole cohort prospective study (Toumi, 2002), which currently has included more than 5000 patients, and as of 21 April 2005 the authorities, following their thorough review of the clinical data, have now recommended a lifting of the restrictions, and sertindole is expected soon to become generally available again.

This article reviews the relationships between antipsychotic drug treatments, prolongation of the QT interval and arrhythmias. Sertindole is an example of a drug for which more recent findings indicate a need to clarify these relationships. Indeed, new data, also from electrophysiological studies with sertindole suggest that counterbalancing mechanisms may act to reduce the risk of proarrhythmic activity arising as a result of QT prolongation. In addition to own literature search and the supplement ‘Sertindole returns as a viable treatment for schizophrenia – a presentation of supporting data’ (International Journal of Psychiatry in Clinical Practice 6, Suppl. 1), the authors read the sertindole product monograph. One author (J.E.) had access to relevant ‘data on file’.

**QT interval prolongation and proarrhythmia**

The QT interval is the duration from the beginning of the QRS complex to the end of the T wave of the electrocardiogram (ECG) (Figure 1) and provides an estimate of the time from the earliest ventricular depolarization to the latest ventricular repolarization. Identification of QT interval prolongation is not always straightforward due to considerable intra- and inter-observer variability (Bednar et al., 2001; Taylor, 2003; Thomas et al., 1996). For example, measurement of the QT interval can sometimes be problematic due to difficulty in discerning the return of the T wave to baseline, particularly if a U wave is present. The QT interval can also vary considerably when recorded simultaneously using different leads. Thus, many clinicians have adopted the practice of measuring the QT interval in either lead II or from the lead with the longest interval (Bednar et al., 2001).

Problems can also arise when comparing QT intervals derived from different computerized ECG systems, as manufacturers use different algorithms to calculate values (Thomas et al., 1996). Another confounding factor is intra-individual variability in the QT interval due to diurnal, prandial, menstrual, postural and other physiological conditions (Browne et al., 1983; Garson, 1993; Morganroth et al., 1991; Taylor, 2003; Thomas et al., 1996). This natural variability can be quite high – for example, in a study of 20 normal subjects, circadian variability was 76 ± 19 ms (mean ± s.d.) from day to night (Morganroth et al., 1991).

Because the duration of the QT interval varies inversely with heart rate, it is necessary to correct the QT interval for the effect of heart rate (QTc), and various formulae have been developed and applied to make this correction (Batchvarov and Malik, 2002; Thomas et al., 1996). However, as these formulae can either over-correct the QT interval when heart rate is high or under-correct when heart rate is low, there is some controversy regarding the most appropriate approach. In the past, Bazett’s formula has been the most widely used (QTcB = QT/RR0.5, where RR is the time interval between two heart beats) (Bazett, 1920). Today, Fridericia’s correction (QTcF = QT/RR0.33) is also...
widely used, and may be more accurate in subjects with marked changes in heart rate (Fridericia, 1920). There is, however, an upcoming trend towards the use of individual- or population-based QTc correction factors in clinical trials that are intentionally designed to assess drug effects on the QT/QTc interval (Batchvarov and Malik, 2002; Malik et al., 2004). Such studies, generally recognized as ‘thorough QT studies’, include multiple baseline ECG recordings, enabling a set of trend analyses to control for factors influencing the duration of the QT/QTc interval, such as pharmacokinetic parameters, circadian and hormonal rhythms, and gender (ICH, 2004).

Standard values for the QTcB interval have been suggested by the FDA (Table 1) (FDA, 2002). A mean drug-induced change in the QTc of 5 ms from drug-free baseline and an individual change in the QTc of >30 ms relative to drug-free baseline measurements are considered to be suggestive of a drug with proarrhythmic potential (ICH, 2004). It is important to recognize, however, that QTc interval prolongation is a manifestation of the primary mechanism by which class III anti-arrhythmic drugs exert their beneficial effect, and to keep in mind that QTc interval prolongation found under physiological conditions is not necessarily harmful.

Although drug-related prolongation of the QTc interval is not unusual, TdP is uncommon (Thomas et al., 1996). However, a markedly long QTc interval (e.g. >500 ms) may be proarrhythmic, allowing the development of TdP. The incidence of TdP is between 1% and 2% for anti-arrhythmic drugs prolonging myocardial repolarization and less than 1:100 000 for non-cardiovascular drugs (Haverkamp et al., 2000). In individual patients, TdP may degenerate into ventricular fibrillation. However, more often, it terminates spontaneously thereby causing syncope.

Mechanisms for drug-induced QT interval prolongation and arrhythmogenesis

The QT interval represents the summation of the duration of ventricular depolarization and repolarization, and is believed to reflect the duration of the cardiac action potential. The duration of the cardiac action potential is controlled by a balance between inward (depolarizing) and outward (repolarizing) currents; action potential prolongation could thus result from either an increase in depolarizing current or a decrease in repolarizing current. The delayed rectifier potassium current (I_K), consisting of rapidly activating (I_Kr) and slowly activating (I_Ks) components each mediated by a distinct ion channel subtype, is thought to play a particularly important role in cardiac repolarization (Hancox et al., 1998; Sanguinetti and Jurkiewicz, 1990).

Available evidence suggests that the basic mechanism by which most drugs prolong the QTc interval is via blockade of potassium currents, particularly I_Kr which is mediated by an ion channel encoded by the human ether-a-go-go-related gene (HERG) (Rampe et al., 1997, 1998; Roy et al., 1996; also see De Ponti et al., 2000 for full review). Almost all drugs that produce a significant degree of QT interval prolongation inhibit I_Kr in electrophysiological studies. Consistent with this, both typical (haloperidol, droperidol, thioridazine, pimozide) and atypical antipsychotics (serindole, risperidone, ziprasidone) have been shown to block either the native HERG-encoded ion channel or its cloned analogue with high affinity (Drolet et al., 1999a,b, 2003; Ekins et al., 2002; Haverkamp et al., 2002; Kang et al., 2000; Rampe et al., 1998; Suessbrich et al., 1997). As a consequence, studies assessing drug affinity to I_Kr/HERG are now routine in all drug development programmes, frequently leading to discontinuation of the development of new drug candidates.

A central question is: how can prolongation of the QT interval lead to life-threatening arrhythmias? A basic theory is that any lack of coordination in the duration of repolarization in neighbouring clusters of myocytes can offset the normal pathways of conductance and allow new alternative cardiac-activating pathways to arise. In the heart there is an intrinsic heterogeneity of action potential duration, giving rise to dispersion of repolarization (Antzelevitch and Shimizu, 2002). A drug that delays myocardial repolarization may amplify this intrinsic spatial dispersion of repolarization, thus creating a potential substrate for the development of re-entry (i.e. return of the same impulse into an already activated zone of heart muscle). Recently it has also been shown that a change in cardiac action potential from a rectangular to a more triangular configuration after treatment with an I_Kr blocker may exaggerate this increase in dispersion (Hondeghem et al., 2001). In addition, however, induction of TdP requires a trigger, in the form of

<table>
<thead>
<tr>
<th>Table 1. Standard values for the QTc interval (Bazett’s correction) suggested by the FDA (FDA, 2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult male (ms)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Borderline</td>
</tr>
<tr>
<td>Prolonged</td>
</tr>
</tbody>
</table>
spontaneous depolarizations, known as early after-depolarizations (EADs), which are generated during the repolarization action potential (Figure 2) (Jones et al., 2001; Yan et al., 2001). The longer the cardiac action potential, the higher the likelihood that EADs may occur.

Thus, it is important to emphasize that QTc prolongation alone is insufficient to cause TdP. It is also necessary to bear in mind that drug effects on other ion channels may counteract the prolongation of the QT interval and the proarrrhythmic drug effect. For example, combined blockade of potassium and calcium channels appear to reduce the proarrrhythmic risk despite a QT interval prolongation in in-vivo models of ventricular arrhythmia (Bril et al., 1996). Consistent with this concept, the combined potassium and calcium channel blocker verapamil has not been associated with reports of TdP even though it blocks \( I_{Kr} \) channels at therapeutic doses (Zhang et al., 1999).

### Risk factors for the development of TdP

Several risk factors for the development of drug-related TdP have been proposed (Table 2) (Haverkamp et al., 2002). Most of them have been derived from case reports or databases on patients who developed TdP associated with particular drugs. Only recently, systematic attempts to identify risk factors for TdP in larger cohorts of patients have been made. In most series, patients developing drug-related TdP were found to have a borderline or prolonged (>440 ms) rate-corrected QT interval at baseline (before drug administration). The fact that the QT interval is usually longer in women compared to men has been suggested to account, at least in part, for the higher prevalence of abnormal QT prolongation and TdP in females. In almost all series of patients with drug-induced TdP, a 2- to 3-fold higher incidence of the arrhythmia in women has been demonstrated. New T wave morphological changes, particularly biphasic T waves, developing independently of pre-existing disturbances of repolarization during therapy with class III agents also seem to represent risk factors for the occurrence of TdP. Bradycardia (e.g. sinus bradycardia, high degree atrioventricular (AV) block, relative bradycardia resulting from post-extrasystolic pauses) and/or low potassium serum concentrations are very common among patients who develop drug-induced TdP. Many reports have demonstrated that these factors alone are capable of inducing TdP. Although drug-induced TdP may occur at subtherapeutic dosages and concentrations (preferentially in combination with low potassium), high drug dosages and concentrations constitute an important risk factor for TdP. The importance of underlying structural heart disease as a potential risk factor for TdP is not clear. Acquired abnormal QT prolongation associated with TdP has been observed in patients with various types of heart diseases as well as in patients without detectable heart disease. Thus, it seems that structural myocardial changes are at least not a prerequisite for this particular form of proarrrhythmia. Although TdP preferentially occurs shortly after initiation of therapy, it may also develop during long-term treatment, in individual cases after several years of treatment. The late occurrence of TdP has been linked to changes in

<table>
<thead>
<tr>
<th>Table 2. Risk factors that favour the genesis of drug-induced abnormal QT prolongation and torsade de pointes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Female gender</td>
</tr>
<tr>
<td>• Bradycardia</td>
</tr>
<tr>
<td>• Prolonged baseline QT</td>
</tr>
<tr>
<td>• Abnormally prolonged QT interval and QTc during drug</td>
</tr>
<tr>
<td>• T wave lability</td>
</tr>
<tr>
<td>• T wave morphology changes during drug treatment</td>
</tr>
<tr>
<td>• Electrolyte disturbances (hypokalaemia, hypomagnesaemia)</td>
</tr>
<tr>
<td>• High drug doses or concentrations</td>
</tr>
<tr>
<td>• Rapid intravenous injection/infusion</td>
</tr>
<tr>
<td>• Use of drugs interfering with the metabolism of drugs known to cause torsade de pointes (e.g. inhibitors of cytochrome P450 enzymes like erythromycin, ketoconazole, and grapefruit juice)</td>
</tr>
<tr>
<td>• Cardiac hypertrophy</td>
</tr>
<tr>
<td>• Diuretic use</td>
</tr>
<tr>
<td>• Recent cardioversion from atrial fibrillation</td>
</tr>
<tr>
<td>• Genetic risk factors, i.e. asymptomatic/symptomatic carriers of mutations encoding for K or Na channels</td>
</tr>
</tbody>
</table>

---

Figure 2. The potential cardiac consequences of QT interval prolongation.
dose, re-initiation of the drug after short discontinuation, new bradycardia, and transient electrolyte disorders like hypokalaemia and/or hypomagnesaemia.

Antipsychotics and QTc interval prolongation

Despite their structural differences, it is now apparent that most classical and atypical antipsychotic drugs can cause dose-related prolongation of the QTc interval, albeit to differing extents. As in a recent review by Titier et al. (2005), the evidence for linking particular antipsychotics with possible TdP is discussed below. The affinity of classical and atypical antipsychotic compounds for D2 dopamine receptors is shown in Table 3.

<table>
<thead>
<tr>
<th>Antipsychotic drug</th>
<th>Classical</th>
<th>New-generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>++++</td>
<td>R</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>++</td>
<td>R</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+++</td>
<td>H</td>
</tr>
<tr>
<td>Droperidole</td>
<td>++++</td>
<td>R</td>
</tr>
<tr>
<td>Pimozide</td>
<td>++</td>
<td>H</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>+</td>
<td>H</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>++</td>
<td>H</td>
</tr>
</tbody>
</table>

Table 3. Affinity of antipsychotic drugs for human (H) or rat (R) dopamine D2 receptors (Hyttel, 1985; Richelson and Souder, 2000; H. Lundbeck, unpublished data)

Dopamine D2 affinity: +, Ki = 100–1000 nM; ++, Ki = 10–100 nM; ++++, Ki = 1–10 nM; +++++, Ki = 0.1–1 nM.

Thioridazine (and mesoridazine)

Abnormal QTc prolongation and TdP appears to be a particular problem with thioridazine, and the drug has been implicated in several cases of sudden death (Kiriike et al., 1987; Mehtonen et al., 1991). In a recent study comparing the effect of different antipsychotics on the QT interval, in individuals with schizophrenia the increase in QTc observed with thioridazine measured 35.6 ms (FDA, 2000). In an Australian study of 299 consecutive patients admitted with neuroleptic poisoning, thioridazine was significantly more likely to abnormally prolong QTc and induce arrhythmias than other neuroleptics including chlorpromazine, trifluoperazine, pericyazine and haloperidol (Buckley et al., 1995). Similarly, a Finnish study of sudden unexplained deaths associated with psychotropic drugs found that phenothiazines, particularly thioridazine, were over-represented when compared with estimates of antipsychotic use in the general population (Mehtonen et al., 1991). Such findings, together with multiple case reports documenting arrhythmias, TdP and sudden death in patients receiving thioridazine, led the Committee on the Safety of Medicines (CSM) in 2000 to restrict the indications for thioridazine in the UK and introduce new contraindications and precautions for safety (CSM, 2000). Similar action was also taken in the USA in the same year (Novartis Pharmaceuticals Corporation, 2000), and mesoridazine was also given a black box warning a few months later. However, thioridazine is argued to have some beneficial effects in comparison to the other classical antipsychotics and, despite these safety precautions, it has earlier been viewed as an atypical antipsychotic drug following early experimental observation on effect on regional dopamine metabolism (Borison and Blowers, 1982), depolarization blocking electrophysiology (Bunney et al., 1973) and the fact that it has a low propensity for inducing extrapyramidal side-effects (EPS).

Haloperidol

Recently, it has been demonstrated that moderate to high doses of the butyrophenone haloperidol (10 mg/day) produce QTc prolongation (Desai et al., 2003). High doses of haloperidol are widely used to control agitation in patients in intensive care units (ICUs). Such patients usually undergo frequent or continuous ECG monitoring, thus providing a valuable additional source of information on the possible link between haloperidol treatment and arrhythmia. So far, there are at least 24 reported cases of haloperidol-induced TdP in ICU patients. In one study, 8 out of 223...
consecutive patients (3.6%) treated with intravenous haloperidol developed TdP (Sharma et al., 1998). However, a number of these severely ill ICU patients had additional risk factors for TdP, and the risk in psychiatric patients treated with haloperidol is probably much lower. In a recent study investigating the long-term safety of 861 aripiprazole-treated patients vs. 433 haloperidol-treated patients, no significant ECG differences were found. Furthermore, rather than increasing, the mean QTc interval decreased in both groups from baseline to end-point (Kasper et al., 2003). Nevertheless, concerns over QTc prolongation with high doses of haloperidol have resulted in a recent reduction in the recommended maximum daily dosage of haloperidol in the UK (BMA, 2002). Results from PET studies suggest a dose of 2–4 mg/d to be appropriate in schizophrenia (Farde et al., 1992).

**Droperidol**

Reilly et al. (2000) showed that psychiatric patients treated with the butyrophenone droperidol have a significantly increased frequency of abnormal QTc prolongation when compared with other antipsychotic drugs. Droperidol also produced a dose-dependent increase in the QTc interval in surgical patients receiving the drug as a pre-anaesthetic agent (Lischke et al., 1994), as well as in in-vitro heart perfusion models (Drolet et al., 1999a). In March 2001, after receiving 72 individual case reports in which QTc prolongation, serious ventricular arrhythmia or sudden death were considered to be associated with droperidol, the manufacturer voluntarily suspended distribution of the drug in the UK (CSM, 2001). In December 2001 a ‘Dear Dr letter’ warning of the risk of TdP associated with this compound was issued in the USA.

**Pimozide**

Pimozide is associated with moderate QTc prolongation, even at a low daily dosage (Fulop et al., 1987), and the drug has been implicated in several cases of sudden death. In the UK during the period 1971–1995, the CSM received 16 reports of death and a further 24 reports of serious cardiac events (predominantly arrhythmias) in patients receiving pimozide (CSM, 1995). As a result, there are now recommendations in both the UK and USA that patients prescribed pimozide periodically undergo ECG monitoring and, if the QTc interval is prolonged, doctors are advised to consider withdrawing the drug or to continue treatment under close supervision (BMA, 2002).

**Sulpiride and amisulpiride**

The substituted benzamides sulpiride and amisulpiride are highly selective for D2-like dopamine receptors. However, there have been some reports of TdP or sudden death with sulpiride (Lande et al., 1992). The information on their effect on the QT interval is very limited.

**New-generation antipsychotics (in order of first registration)**

**Clozapine**

Abnormally long QTc values are rarely observed with clozapine in clinical practice. For example, in a study of 61 clozapine-treated patients, only two had a QTc value greater than 500 ms (Kang et al., 2000). Furthermore, there have not been any unequivocal reports of a fatal cardiac arrhythmia in patients receiving clozapine. A recent review of the manufacturer’s database found that all but three reports of QTc prolongation and the two reports of TdP at therapeutic doses of clozapine were confounded by relevant co-medication/comorbidity (Warner and Hoffman, 2002).

**Risperidone**

In early clinical studies, risperidone appeared to have a minimal effect on the QTc interval at therapeutic doses. However, in the 054 study, a comparison of ECGs from patients on different antipsychotics found a mean increase in the QTc interval of \( \gamma \) 11.6 ms at the maximum recommended dosage of 16 mg/d (Figure 3) (FDA, 2000). There are no cases of TdP associated with risperidone treatment in the literature.

**Sertindole**

The atypical antipsychotic sertindole was initially launched in 1996 within the European Union. Because a potential to prolong the QTc interval had been noted early in the development, sertindole ECGs were studied and scrutinized extensively for potential effects. Subsequently an unusually high occurrence of cardiac arrhythmias and cardiac deaths were reported in patients on sertindole treatment. This chain of events was initiated by the UK Adverse Drug Reactions Online Information Tracking (ADROIT) database, and it led to sertindole being referred to the CPMP, and finally in 1998, to the suspension of sertindole in four European countries. Concerns regarding the QTc interval prolongation and a possible increased risk of serious arrhythmias in patients on sertindole made the
Figure 3. Comparison of mean QTcB (Bazett-corrected QT) changes from baseline to steady state (or, for sertindole, at last assessment) for different antipsychotics at high doses. Data for ziprasidone (Zip, n = 31), risperidone (Ris, n = 25), olanzapine (Olz, n = 24), quetiapine (Que, n = 27), thioridazine (Thi, n = 30) and haloperidol (Hal, n = 27) are taken from Pfizer study 054 and are derived from ECG measurements taken at time of steady-state peak plasma concentration (FDA, 2000). Sertindole data are from short-term clinical studies with a fixed dose of 24 mg, which is the maximum recommended dose, given in exceptional cases only (n = 262).

manufacturer, H. Lundbeck A/S, decide to withdraw sertindole, for precautionary reasons.

However, doubts concerning the perceived link between the QTc interval and arrhythmias and more particularly concerning the actual existence of an increase in cardiac mortality and morbidity in patients treated with sertindole prompted the manufacturer to perform further thorough investigations. Data from subsequent epidemiological studies of sertindole vs. other atypical antipsychotic drugs did not support the ADROIT signal. This evidence was reinforced by further analyses of the clinical trial database and substantial preclinical evidence.

In a retrospective analysis, a subset of nearly 2000 ECGs from phase II/III studies of sertindole was selected for re-reading and comparison with original data. The subset consisted of all ECGs from 17 studies that were identified with an originally overread value of QT, QTcB, and/or QTcF of ≳500 ms during sertindole treatment. In addition the reanalysis included all ECGs from patients treated with either placebo or 20 mg sertindole in two pivotal studies (M93-098 and M93-113) (Lundbeck data, on file). In the 17 phase II/III studies, a total of 305 ECGs were identified as having a QT, QTcB, and/or QTcF value ≳500 ms. For 27 of these ECGs, the QT interval could not be re-read when selected for a retrospective analysis. This was mainly due to poor quality of the ECG strips. The remaining 278 re-read ECGs used for retrospective analysis were recorded in 159 patients. Of note, and the reason why this retrospective analysis is considered interesting, is that the sertindole studies submitted for regulatory review in 1995 actually reported the longest QT/QTc interval in any of the 12 leads of the ECG. Subsequently, the methodology used to assess the durations of the QT interval changed in many laboratories. In the majority, the methodology applied was a single lead measurement, typically in lead II. The result of the sertindole retrospective analysis of the re-reading of QT/QTc intervals in lead II showed that only two of the original 278 ECGs still had QTc values above the signal value of 500 ms. In fact, values above 500 ms were only present when applying the Bazett QTc correction formulae. While the data from the re-readings gave insight into the effect of the methodology used, a clinically significant effect of sertindole on QTc prolongation was still present following re-readings at currently applied methodology. In the retrospective reading of the QT interval in lead II, sertindole (20 mg) prolonged QTcF by 20 ± 26 ms (mean ± S.D.; n = 160 vs. a study-matched re-read placebo group with QTcF = −5 ± 22 ms; n = 162). Thus, although sertindole was a drug that initiated the focus on QTc prolongation, the present re-analysis by today’s standards does not clearly show that sertindole stands out as particularly prone to induce QTc prolongation.

In October 2001, after considering the new findings described in later sections of this review, the CPMP decided that sertindole could be conditionally reintroduced with the commitment by H. Lundbeck A/S to ensure that all sertindole patients were exclusively recruited to a post-marketing surveillance study for the first year (MCA, 2002), which has then resulted in the inclusion of an additional 5000 patients in this study confirming that Serdolect® can be prescribed safely. And on evaluating available data the recent decision of EMEA was to recommend that sertindole may become generally available again.

Olanzapine

In the 054 study there was a 6.8 ms QTc prolongation with olanzapine (Figure 3). No case of TdP has been published. In a combined analysis of data from four clinical trials involving a total of 1342 olanzapine-treated patients, the incidence of the maximum QTc being greater than 450 ms during treatment was approximately equal to that at baseline (Czekella et al., 2001). These data suggest that at therapeutic doses,
olanzapine does not normally produce QTc prolongation.

Ziprasidone

Although ziprasidone is now licensed in Europe and the USA, concerns over its effect on the QTc interval led to delays in marketing approval for the drug in the USA. The 054 study (FDA, 2000), comparing ECGs from patients on different antipsychotics found a mean increase in the QTc interval of ~20 ms at the maximum licensed dosage of 160 mg/d (Figure 3) (FDA, 2000). Reflecting the initial concerns, USA prescribing information for ziprasidone specifies that the drug is contraindicated in patients with a known history of QT prolongation, recent myocardial infarction or uncompensated heart failure, and should not be co-prescribed with other QT-prolonging drugs (Pfizer, 2001).

Quetiapine

In the 054 study, quetiapine prolonged QTc by 14.5 ms (Figure 3) (FDA, 2000). However, prolongation of the QTc interval (>500 ms) has been reported following quetiapine overdose, either alone (Gajwani et al., 2000), or in combination with risperidone treatment (Beelen et al., 2001). Further support for a dose–response effect is given by observations after co-administration of drugs that produce increased plasma levels of quetiapine by inhibiting its metabolism (e.g. lovastatin) (Furst et al., 2002).

Aripiprazole

As mentioned above, no significant QTc interval increases from baseline were found in a study of 861 patients treated with aripiprazole and 433 treated with haloperidol (Kasper et al., 2003).

Summary: QTc prolongation by antipsychotic drugs

The evidence described above shows that, as would be expected from their wide structural diversity, the different antipsychotic agents differ in their propensity to prolong the QTc interval. The 054 study referred to above has recently been re-reported by Harrigan et al. (2004) quoting slightly smaller values for the QTc change for each drug, but showing the same pattern of variability in effect. This variability has also been confirmed in vitro. Drici and colleagues (1998) compared the potency of haloperidol, risperidone, sertindole, clozapine and olanzapine in prolongation of the QT interval in the perfused isolated feline heart. All five drugs prolonged the QT interval in a dose-dependent manner, and comparison of their dose–response curves indicated that haloperidol and risperidone were significantly more potent than the others. However, these two drugs also have high affinity for the D2 dopamine receptor, which is the target for antipsychotic effect. The comparatively low doses required for therapeutic effect are, thus, the likely reason for limited QT prolongation at therapeutic doses.

The validity of reports on arrhythmias in clinical studies

The processes for reporting of arrhythmias in clinical studies, as well as in pharmacovigilance, may vary and are important to consider when comparing drugs in large-scale clinical trials and in post-marketing studies conducted under conditions of normal clinical practice. It is impossible to have ECG monitoring for 24 h a day. As a result, in reports of death we usually have to rely on clinical judgements without having an ECG that can substantiate the presence of arrhythmia.

All-cause mortality is the ultimate end-point reported in most clinical trials and post-marketing studies. The subcategory of sudden death is highly relevant, although events unrelated to arrhythmias or TdP are also categorized as sudden death. Sudden cardiac death is a more specific concept. This is generally defined as death from unexpected circulatory arrest, usually due to a cardiac arrhythmia and occurring within an hour after the onset of symptoms. This end-point still does not correspond only to mortality arising from arrhythmia/TdP, since other causes of sudden cardiac death, such as myocardial infarction, are also included. Nevertheless, reports of a higher incidence of sudden death for a particular antipsychotic would be grounds for serious concern, regardless of the underlying mechanism. In this respect, it is also worth bearing in mind that TdP is a rare event and so would be expected to be absent from most clinical trials and only come to light in larger post-marketing studies.

Following the voluntary withdrawal of sertindole from the market in 1998 in response to concerns that the drug’s effect on QTc could cause serious and fatal ventricular arrhythmias, the manufacturer has conducted a series of electrophysiological and epidemiological studies to examine the problem in detail. Interestingly, as suggested from the studies reviewed below, although sertindole can prolong the QTc interval, the drug has low proarrhythmic potential and cannot be associated with increased mortality. No other atypical antipsychotic drugs have yet been as
well studied as sertindole in this respect, and it is not yet known whether any of them also have a lower than expected proarrhythmic potential.

Recent evidence concerning sertindole

Epidemiological studies

In a manufacturer-independent prescription event monitoring programme (PEM), the mortality rate was examined in all patients receiving sertindole, olanzapine or risperidone prescribed by general practitioners in the UK (Wilton et al., 2001). Of the three drugs, sertindole had the lowest SMR. This observation called for a comparison of the death rates in the original ADROIT database with those in the PEM study for the same period. This comparison revealed a bias in the ADROIT database. When compared with olanzapine or risperidone treatment, a much higher percentage of the deaths occurring during sertindole treatment were captured by the ADROIT database. Thus, the original ADROIT alert reflected differences in the pattern of reporting for the three drugs rather than differences in the death rate. A second PEM study based on prescriptions issued by psychiatrists through 25 hospital pharmacies in the UK reached a similar conclusion. The mortality rate during sertindole treatment in a specialist setting was not different to the mortality rates associated with olanzapine or risperidone treatment (Branford et al., 2003) (Table 4).

Several epidemiological studies performed in Europe have reached similar conclusions. In the sertindole European Safety and Exposure Survey (ESSES), involving 8608 patients receiving sertindole in routine practice in six European countries, the all-cause mortality rate was lower than that observed in clinical trials (Peuskens et al., 2003) (Figure 4). Following the market suspension of sertindole, most of the patients in the ESES study were switched to other antipsychotics, which provided the opportunity to conduct a retrospective comparative cohort study involving around 1112 sertindole-treated patients. In this comparative mortality study, all-cause and cause-specific mortality rates were consistently lower during treatment with sertindole than after stopping the drug, or during treatment with other antipsychotics (Sturkenboom et al., 2001). The adjusted relative risk of cardiac mortality was 30% lower during sertindole treatment.

Until the temporary marketing suspension of sertindole in 1998, a referenced, observational, cohort safety study of sertindole in the treatment of patients with schizophrenia – the European Post-marketing Observational Serdolect (EPOS) Study – was ongoing in 10 European countries. Among the 2321 patients included in this study, the mortality rate (excluding suicide) for the group receiving sertindole was almost half that of the non-sertindole group (Moore, 2002). Patients in the sertindole cohort in this study continued to be followed after sertindole treatment was stopped, allowing application of the comparative cohort concept used in the comparative mortality study (Sturkenboom et al., 2001). Again, all-cause mortality during sertindole treatment was found to be lower than that during post-sertindole treatment (Moore, 2002).

Following its temporary marketing suspension, sertindole remained available in Europe under a specific named-patient use programme in which patients were closely monitored. This provided the opportunity to conduct a multicentre retrospective survey of the occurrence of serious adverse events in a large cohort of sertindole-treated patients under circumstances in which it was unlikely that any serious adverse events would go unreported. In the Sertindole Safety Survey (SSS) involving 1444 patients in 11 European countries, the all-cause mortality rate for sertindole-treated patients was lower than that observed in the clinical trials and lower than that for other reference populations in post-marketing studies (Toumi et al., 2003). Furthermore, although QT interval prolongation was the second most common adverse event with 15 occurrences, there were no recorded cases of TdP.

Taken together, the results of a series of different epidemiological studies consistently point towards equal or lower mortality rates, including cardiac deaths, for sertindole compared with other antipsychotic

### Table 4. All-cause mortality rates for sertindole, risperidone, olanzapine, and pooled risperidone and olanzapine data from the UK Hospital Pharmacy Study (Branford et al., 2003)

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Patients</th>
<th>Patient years of exposure</th>
<th>No. of deaths (total)</th>
<th>All-cause mortality rate (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertindole</td>
<td>184</td>
<td>143</td>
<td>2</td>
<td>1.40 (0.17–5.06)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>294</td>
<td>244</td>
<td>7</td>
<td>2.87 (1.15–5.91)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>363</td>
<td>382</td>
<td>3</td>
<td>0.79 (0.16–2.30)</td>
</tr>
<tr>
<td>Pooled risperidone and olanzapine data</td>
<td>657</td>
<td>626</td>
<td>10</td>
<td>1.60 (0.77–2.94)</td>
</tr>
</tbody>
</table>

Antipsychotic drugs and QTc
drugs (Figure 5) and refute the original concern raised by the ADROIT database.

**Experimental studies**

The mechanism by which sertindole induces QTc prolongation is via inhibition of the delayed rectifier potassium channel ($I_{Kr}$ or $I_{HERG}$). Sertindole blocks the rapid component of the human rectifier potassium channel with an IC$_{50}$ of 3–107 nM, depending on assay conditions (Kongsamut et al., 2002; Rampe et al., 1998; Thomsen et al., 2003). The high-affinity binding of sertindole to $I_{Kr}$ is both use and frequency dependent, and sertindole does not easily dissociate from the protein with drug washout. However, the actual recognition site at which sertindole binds to the $I_{Kr}$...
protein has not been finally identified. In agreement with recent scientific literature on \( I_{Kr} \) channel-binding sites, sertindole is believed to cross the cell membrane in its neutral form and act at a site within the pore region of the potassium channel (Finlayson et al., 2001; Ishii et al., 2003). Sertindole also exerts an inhibitory action on other ion channels such as \( I_{Ca} \) (Thomsen et al., 2003). However, as the inhibitory actions on these ion channels require micromolar concentrations in vitro, they are of questionable clinical relevance.

Notwithstanding that sertindole is a blocker of \( I_{Kr} \), experimental evidence suggests that the sertindole molecule may reduce proarrhythmia in multicellular preparations (Drici et al., 1998; Eckardt et al., 2002; Thomsen et al., 2003). Although the exact nature of this counter-regulatory property is not known, it may in theory be related to mixed ion-channel inhibition or possibly to \( \alpha_1 \)-adrenergic antagonism of sertindole.

In rabbit cardiac Purkinje fibres, the cardiac action potential is moderately prolonged by sertindole concentrations of 100–300 nm. (Haverkamp et al., 2002). The effects of sertindole do not resemble the effect of a \( K_r \) blocker, such as dofetilide. Additionally, in the cardiac rabbit Purkinje fibre model, sertindole did not trigger EADs or proarrhythmic features.

Sertindole has been tested both in the sinus-paced isolated feline heart (Drici et al., 1998) and also in the isolated AV-node ablated rabbit heart (Eckardt et al., 2002). However, in the feline heart, sertindole was shown to be less potent in prolonging the QT interval than the antipsychotic drugs risperidone and haloperidol. In the AV-node ablated rabbit heart, sertindole failed to induce TdP, despite a similar magnitude of QT prolongation to the reference compound D,L-sotalol. Additionally, sertindole did not induce TdP despite the experimental introduction of severe hypokalaemia (1.5 mmol) and bradycardia, both of which are recognized risk factors for TdP. In the isolated heart preparation, sertindole displayed a profile that was not typical of a pure \( I_{Kr} \) blocker, indicating that sertindole possesses ancillary properties that prevent TdP. Sertindole did not induce EADs, and unlike the \( I_{Kr} \) blocker D,L-sotalol, sertindole did not increase transmural dispersion of repolarization, all of which are believed to be associated with proarrhythmic activity.

Sertindole has also been evaluated in an animal model of TdP in vivo (Thomsen et al., 2003). In this model, dogs undergo surgical ablation of the AV node causing double-sided cardiac hypertrophy and electrical remodelling of the heart (Vos et al., 2001). These dogs become highly susceptible to TdP arrhythmia, with a spontaneous frequency of TdP and sudden death in \( \sim 10\% \) of the AV-node ablated dogs at baseline (Van Opstal et al., 2001). With the challenge of a pure \( I_{Kr} \) blocker like dofetilide or azimilide, very low doses cause reproducible events of TdP arrhythmia (Van Opstal et al., 1999). In this sensitive model, sertindole was administered in two dosing regimes. First, normal and AV-node ablated dogs were challenged with a therapeutic plasma concentration (50–200 nmol/l). Hereafter, a second set of AV-node ablated dogs were challenged with toxic doses of sertindole at plasma concentrations higher than 500 nmol/l. The results of these investigations revealed that sertindole, in comparison to the pure \( I_{Kr} \) blocker dofetilide, caused less QTc prolongation at similar plasma concentrations (which for both drugs were considered to be therapeutic plasma concentrations).

To reach a similar magnitude of QTc prolongation as dofetilide, sertindole had to be administered at the high plasma level of 3000 nmol/l. At this high level, sertindole did produce TdP arrhythmia in dogs with AV-node ablation, when the dogs were loaded to toxic plasma concentrations of \( \sim 1100 \) nm. Importantly, there was no incidence of TdP at therapeutic plasma concentrations of sertindole. This study clearly demonstrated that QT/QTc prolongation by sertindole is not in itself sufficient to promote TdP arrhythmia. Sertindole clearly caused a significant increase in the QTc interval even at therapeutic dosing; however, it required toxic doses to promote TdP arrhythmia.

As described in the previous section, electrophysiological studies conducted in animal models of proarrhythmia suggest that sertindole-induced QTc prolongation is not sufficient to promote serious and fatal ventricular arrhythmias (Figure 2). Additional inherent properties in the sertindole molecule may possibly protect from the occurrence of such effects and it may require unique circumstances to promote ventricular arrhythmias with sertindole. Although the extrapolation of animal findings on QT prolongation and arrhythmias to human subjects must be undertaken with caution due to significant species differences, the animal data are consistent with the clinical epidemiological studies reviewed above.

**Benefit/risk considerations with antipsychotic drugs**

When selecting an antipsychotic for an individual patient, the risk of sudden death and arrhythmia associated with QTc prolongation should be viewed in
the context of the overall risks, particular risk factors (Table 2), and benefits of each treatment. Obviously, it would be prudent to avoid drugs with a significant effect on QTc unless there are clear efficacy benefits and/or robust data to show that QTc prolongation does not pose an increased mortality risk. A minimum clinical recommendation is that no matter which antipsychotic drug the physician decides to prescribe, conventional or non-conventional, the patient should always be asked if he/she has a known heart condition, was ever prescribed any medication for the heart or against high blood pressure, or if he/she has ever fainted. If the reply to any of these questions is affirmative, the patient must have an ECG examination before the start of antipsychotic treatment.

Concluding remarks

Most conventional and atypical antipsychotics can prolong the QTc interval and in some cases these drugs have been implicated in TdP and sudden death. It is, therefore, prudent to prescribe antipsychotic drugs with a significant effect on QTc only if there are clear efficacy benefits and/or robust data to show that QTc prolongation does not pose an increased mortality risk. Accumulating evidence suggests that the risk of QTc prolongation and arrhythmias is not the same for all antipsychotics. It is now becoming clear that there is not a direct relationship between the extent of drug-induced QTc prolongation and the risk of arrhythmia or death. Studies with a wide range of drugs other than antipsychotics indicate that QTc prolongation alone is not proarrhythmic, and that both a substrate (increased heterogeneity of action potential duration of different cardiac cell types) and a trigger (EAD) are required for the development of arrhythmia. For at least one of the atypical antipsychotics, sertindole, QTc prolongation occurs without the necessary substrate or trigger for arrhythmogenic activity; thus, QTc prolongation in itself is not predictive for the development of life-threatening arrhythmias with this drug. Several epidemiological studies support this view. At the present time, sertindole is the only atypical antipsychotic drug that has been extensively studied in this regard, and it remains to be seen whether other drugs in this class also have a lower than expected proarrhythmic potential.

Acknowledgements

The writing of this article was initiated by H. Lundbeck A/S, identifying a need for a review about cardiac effects of antipsychotics (particularly on the QTc interval), aimed towards a psychiatric readership. Professor Farde, who is on the IJNP editorial board, supported the idea, and expressed an interest in participating in the writing. He was not involved in any aspect of the review process.

Statement of Interest

Professor Lindström’s position since 1985 has been at the Department of Neuroscience, Psychiatry, at Uppsala University, where she is now chief physician at the Clinic for Psychosis and Rehabilitation. Professor Lindström has held lectures for and received honoraria from Jansen-Cilag and Pfizer. Professor Lars Farde holds the Chair of Psychiatry at the Karolinska Institute and is a former member of the H. Lundbeck international advisory board for antipsychotics, he is now engaged on drug discovery at AstraZeneca, Stockholm. Jonas Eberhard has held lectures for and received honoraria from Jansen-Cilag and Pfizer. In addition to his affiliation at the Department of Psychiatry at Lund University, he is currently (since the end of 2001) employed as a medical advisor for H. Lundbeck A/S in Copenhagen. Professor Haverkamp has held lectures for and received honoraria from H. Lundbeck and Pfizer. He has also been part of the Sertindole international advisory board.

References

lengthens cardiac repolarisation due to block of the rapid component of the delayed rectified potassium current. *Journal of Cardiovascular Electrophysiology* 10, 1597–1604.


patients in Europe. *Schizophrenia Research* 60 (Suppl. 1), 364–365.  


**Toumi M, Anquier P, Francois C** (2003). The safety and tolerability of sertindole in a patient name use programme. *Schizophrenia Research* 60 (Suppl. 1), S68.


