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### Recent studies on ECG changes, antipsychotic use and sudden death in psychiatric patients

Sudden unexplained death has been linked with anti-psychotic drugs since soon after their discovery, but in the intervening four decades no consensus has been achieved on its frequency, or even whether a true causal association exists. A College working group on the issue had to conclude that 'There is uncertainty regarding the mechanisms underlying sudden death . . . and a lack of any systematic data relevant to an individual patient's risk, or the relative risk with various antipsychotics.' (Royal College of Psychiatrists, 1997: p. 22) The paucity of research evidence has prevented us from resolving the dilemma of how to balance the unknown risk of a rare but lethal adverse reaction against the undoubted and lifesaving benefits of long-term treatment. Now research into the cardiotoxic effects of antipsychotic drugs is bringing molecular biology together with epidemiological approaches to clarify both the mechanism and the clinical relevance of sudden death as a potential complication of the treatment of the mentally ill.

Drug-induced arrhythmia is a feasible mechanism by which antipsychotic drugs may increase the risk of sudden death. Some antipsychotics are associated with QT interval prolongation on the electrocardiogram (ECG), which increases risk of sudden death in other populations from the potentially fatal ventricular arrhythmia known as torsade de pointes. Thioridazine has been linked most frequently with these effects, but the problem is not confined to conventional neuroleptics, as demonstrated by the voluntary withdrawal of the atypical antipsychotic sertindole owing to reports of both QT changes and sudden death, which is pending further safety data. These effects are unrelated to brain receptor binding profiles. What these drugs have in common is an action to prolong cardiac repolarisation via blockade of the delayed rectifier potassium channel ( $I_{kr}$ ) within the heart (Yap & Camm, 2000). The cloning of the human 'ether-a-go-go' (HERG) gene that encodes for this channel has resulted in studies confirming the specific  $I_{kr}$  blocking potential of haloperidol, droperidol, pimozide and sertindole. Antipsychotics bind to the  $I_{kr}$  with varying affinities, which may prove to be associated with their potential for arrhythmogenesis. Animal studies of  $I_{kr}$  blockade with thioridazine have shown a concentration dependent effect. Hence the prospect now exists for

newly developed antipsychotics to be screened by manufacturers for their relative potential to block  $I_{kr}$ , and to be excluded if affinity is high.

$I_{kr}$  blockade may be necessary for drug-induced QT prolongation and subsequent arrhythmia, but other factors also play a critical role. Although increasing anti-psychotic dose has been linked to QT prolongation in psychiatric patients (Warner *et al*, 1996), other factors may operate, creating high-risk groups who develop QT prolongation and arrhythmias even at low doses. Old age, female gender and pre-existing ischaemic heart disease are all likely to increase risk. Hypokalaemia reduces the  $I_{kr}$  current, raising the likelihood that drug-induced QT prolongation will progress to arrhythmia. Metabolism of most psychotropic drugs is genetically determined, leading to differences of up to fivefold in steady state plasma levels. In the case of thioridazine, mutations of the gene coding for the CYP2D6 hepatic cytochrome p450 isoenzyme (debrisoquine hydroxylase) can result in accumulation of metabolites that may be cardiotoxic. Pharmacodynamic variation may also determine risk. Mutations at the HERG locus produce a congenital 'long QT' syndrome (LQT2) in which  $I_{kr}$  current is reduced and torsade de pointes is frequent. Further blockade by drugs may then trigger the arrhythmia. Rare LQT2 homozygotes may be most vulnerable, but heterozygotes are now being identified who may also be at increased risk. Furthermore, the QT interval in normal individuals is substantially genetically determined by a limited number of alleles at LQT2 and other LQT2 loci, raising the possibility that there may be substantial subgroups of the population at higher risk of drug-induced torsade de pointes. The prescription of two or more psychotropic drugs is common in psychiatric practice and interactions may increase the likelihood of a clinically significant effect. Tricyclic antidepressants also prolong the QT interval and block  $I_{kr}$  (Baker *et al*, 1997; Teschemacher, *et al*, 1999), but even some of the relatively non-cardiotoxic selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and fluvoxamine can act to inhibit metabolism at CYP2D6, resulting in substantial increases in anti-psychotic drug levels and a higher risk of QT prolongation and torsade de pointes (Carrillo *et al*, 1999).



How are these theoretical risks translated into real clinical practice? Two recent epidemiological studies have sought to clarify the relative risk of corrected QT (QTc) prolongation and sudden unexplained death itself in psychiatric patients. First, an electrocardiographic survey of 495 patients on a variety of psychotropic medication revealed a robust association between prolonged QTc and increasing doses of antipsychotic drugs. The association was particularly strong for the specific antipsychotics thioridazine (odds ratio 5.4; 95% CI 2.0–13.7) and droperidol (odds ratio 6.7; 95% CI 1.8–24.8). Other risk factors were age over 65 years and treatment with tricyclic antidepressants (Reilly, et al, 2000). Second, a matched case–control study of sudden unexplained death in psychiatric in-patients over a 12-year period in the north-east of England has now been completed. Preliminary data suggest an association between sudden death and thioridazine. Other independent predictors were hypertension and ischaemic heart disease (Reilly, et al, 2001). The absolute incidence of sudden unexplained death was low at only one per 1000 bed years for patients under 65 years (12/1000 bed years for those over 65 years), representing 5% of total in-patient deaths.

Although both studies require replication and extension into wider populations, they provide further evidence for a specific cardiotoxic effect of thioridazine, which exceeds that of other antipsychotic drugs. Although the end-points of arrhythmia and sudden death are rare, thioridazine's cardiotoxicity is of major clinical importance. In 1999, thioridazine was the most widely prescribed antipsychotic by general practitioners in England (Prescription Pricing Authority, 1999). It is rarely now a primary treatment for schizophrenia, but is frequently used for anxiety disorders across the age range, and for behavioural problems in the elderly with dementia, in preference to benzodiazepines. It is also used as adjunct therapy in agitated depression, in combination with tricyclics or SSRIs. There is little randomised trial evidence for these indications, and a recent Cochrane Review concluded that it had no place in the treatment of dementia (Kirchner et al, 2001). Thioridazine is more cardiotoxic in overdose than other antipsychotic drugs (Buckley et al, 1995). Low doses, as are often used in the elderly, do not necessarily reduce risk; both QTc prolongation and sudden unexplained death were found in association with doses less than 75 mg per day (Reilly et al, 2000, 2001). Its use in depression necessitates combinations with other drugs that may amplify its cardiotoxicity by additive (tricyclic) or enzyme inhibiting (SSRI) effects. Electrocardiography prior to initiation of drug therapy and during therapy may detect some patients at higher risk owing to pre-existing repolarisation abnormalities or ischaemia and those with marked repolarisation abnormalities during treatment. However, interpretation of ECGs and QT intervals is difficult for non-specialists and as yet there is no evidence that screening would reduce the incidence of arrhythmia or sudden death, in contrast, for example, to the effect of haematological screening in clozapine therapy. The US Food and Drug Administration (Food and

Drug Administration, 2000) took action in June 2000 to restrict the use of thioridazine in patients with schizophrenia who are intolerant of, or have failed to respond to, other drugs, and have recommended that ECGs are performed before and at intervals during therapy. Co-prescription with inhibitors of CYP2D6 is now contraindicated in the US. The Committee on Safety of Medicines has now taken action to advise doctors in the UK to restrict thioridazine to second line treatment for schizophrenia, and to introduce baseline screening (Committee on Safety of Medicines & Medicines Control Agency, 2001).

Sudden unexplained death in psychiatric patients is uncommon, but many deaths may go unrecognised. A higher index of suspicion and a lower threshold for the seeking of a postmortem examination are required. A proportion of sudden deaths may be related to antipsychotic-induced torsade de pointes and thioridazine is particularly implicated. This is a rare adverse drug reaction, the risk of which may be outweighed for most antipsychotic drugs by their benefits, but an individual assessment is required for each drug as to whether it can be used safely, and whether restrictions are necessary. Current studies cannot reassure us that significant risks do not exist with other antipsychotic drugs. The identification of the HERG gene will allow screening and exclusion of new antipsychotics prior to clinical trials, but there is a need for more extensive pharmacoepidemiological studies of current drugs, looking both at QT abnormalities and sudden death itself. In the UK the Confidential Inquiry into Suicide and Homicide has now been expanded to examine risk factors for sudden unexplained deaths in psychiatric hospitals on a national basis (Appleby et al, 2000). The help of psychiatrists will be invaluable in clarifying the frequency and risk factors for this uncommon but devastating adverse drug reaction.

## Declaration of interest

J.G.R has received speaker fees from Eli Lilly and Janssen–Cilag for lectures on the cardiac side-effects of antipsychotics and has received fees from AstraZeneca for chairing academic meetings. S.H.L.T has done research funded by manufacturers of antipsychotic drugs (Pfizer) and has been paid consultancy work for manufacturers of antipsychotic drugs (Lundbeck, Pfizer). I.N.F has received speaker fees and has been on advisory panels for a number of companies marketing antipsychotics, including Eli Lilly, AstraZeneca, Janssen–Cilag and Pfizer.

## References

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| <p>APPLEBY, L., SHAW, J., AMOS, T., et al (2000) Sudden unexplained death in psychiatric in-patients. <i>British Journal of Psychiatry</i>, <b>176</b>, 405–406.</p> <p>BAKER, B., DORIAN, P., SANDOR, P., et al (1997) Electrocardiographic effects of fluoxetine and doxepin</p> | <p>patients with major depressive disorder. <i>Journal of Clinical Psychopharmacology</i>, <b>17</b>, 15–21.</p> <p>BUCKLEY, N. A., WHYTE, I. M. &amp; DAWSON, A. H. (1995) Cardiotoxicity more common in thioridazine overdose</p> |
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- than with other neuroleptics. *Journal of Toxicology. Clinical Toxicology*, **33**(3), 199–204.
- CARRILLO, J. A., RAMOS, S. I., HERRAIZ, A. G., et al (1999) Pharmacokinetic interaction of fluvoxamine and thioridazine in schizophrenic patients. *Journal of Clinical Psychopharmacology*, **19**(6), 494–499.
- COMMITTEE ON SAFETY OF MEDICINES & MEDICINES CONTROL AGENCY (2001) QT interval prolongation and antipsychotics. *Current Problems in Pharmacovigilance*, **27**, 4.
- FOOD AND DRUG ADMINISTRATION (2000) *Supplemental New Drug Applications for Mollaril (Thioridazine)*. Rockville, MD: US Department of Health and Human Services (<http://www.fda.gov/cder/ogd/rld/17923s48.pdf>).
- KIRCHNER, V., KELLY, C. A. & HARVEY, R. J. (2001) A systematic review of the evidence for the safety and efficacy of thioridazine in dementia (Cochrane Review). In *The Cochrane Library*, **4**. Oxford: Update Software.
- PRESCRIPTION PRICING AUTHORITY (1999) *Prescribing Cost Analysis Report 1999*. (<http://www.doh.gov.uk/stats/pca99.htm>) London: Department of Health.
- REILLY, J., AYIS, S., FERRIER, I., et al (2000) QTc interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet*, **355**, 1048–1052.
- , —, —, et al (2001) Sudden death and thioridazine (abstract). *British Journal of Clinical Pharmacology*, **51**, 363.
- ROYAL COLLEGE OF PSYCHIATRISTS (1997) *The Association Between Antipsychotic Drugs and Sudden Death. Report of the Working Group of the Royal College of Psychiatrists Psychopharmacology Sub-Group*. Council Report CR57. London: Royal College of Psychiatrists.
- TESCHEMACHER, A. G., SEWARD, E. P., HANCOX, J. C. et al (1999) Inhibition of the current heterologously expressed HERG potassium channels by imipramine and amitriptyline. *British Journal of Pharmacology*, **128**(2), 479–485.
- WARNER, J., BARNES, T. & HENRY, J. (1996) Electrocardiographic changes in patients receiving neuroleptic medication. *Acta Psychiatrica Scandinavica*, **93**, 311–313.
- YAP, Y. & CAMM, J. (2000) Risk of torsade de pointes with non-cardiac drugs. *BMJ*, **320**, 1158–1159.
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