

## Sudden unexplained death in psychiatric in-patients

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Reports of sudden death in people with mental illness who are taking antipsychotic medication have been a source of public and professional controversy for three decades. Psychiatric patients are at increased risk of death from a number of natural causes, including cardiovascular disease (Sims & Prior, 1980; Baxter, 1996; Hansen *et al*, 1997; Harris & Barraclough, 1998; Ruschena *et al*, 1998). Because many sudden deaths are the result of coronary artery disease, an increase in sudden deaths would be expected by this mechanism alone. However, cases of sudden death in young patients and recent evidence in schizophrenia of a high rate of sudden death without explanatory post-mortem findings suggest that factors other than coronary artery disease are contributory (Ruschena *et al*, 1998). In 1997 a report by an expert committee convened by the Royal College of Psychiatrists recommended a large-scale systematic study of the relationship between psychotropic drugs and sudden death (Royal College of Psychiatrists, 1997). Such a study has now begun; psychiatrists throughout England and Wales will be asked to take part and one purpose of this paper is to explain how it will be conducted.

### CARDIAC EFFECTS OF ANTIPSYCHOTIC DRUGS

The mechanism by which antipsychotic drugs may cause sudden death is by inducing cardiac arrhythmias, because they are known to disturb normal cardiac electrophysiology, resulting in electrocardiogram (ECG) changes. Their actions are similar to those of the anti-arrhythmic drug quinidine, and include sodium channel blockade and delay to ventricular repolarisation (Arita & Surawicz, 1973). Severe sodium channel blockade may be clinically important after poisoning with antipsychotic drugs and appears on the ECG

as broadening of the QRS complex, reflecting reduced conduction velocity through the specialist conducting tissue in the bundle of His. Delayed ventricular repolarisation is probably more important because it can be detected after therapeutic doses of antipsychotic drugs. It appears on the ECG as abnormalities of the T wave, prominent U waves and/or prolongation of the QT interval. This is the interval between the onset of ventricular depolarisation and the end of ventricular repolarisation. The QT interval shortens with increasing heart rate and is often adjusted for this to produce a corrected QT interval, or QTc (Thomas, 1994).

These changes might, in extreme cases or in susceptible individuals, lead to malignant ventricular arrhythmias, particularly a multifocal ventricular tachycardia termed *torsade de pointes*. This is usually self-limiting, causing dizziness or syncope, but may generate into ventricular fibrillation and cause sudden death (Thomas, 1994). The importance of this mechanism has been highlighted recently by the withdrawal of sertindole, an atypical antipsychotic, because of its propensity to cause QT interval prolongation, and following reports of arrhythmias and sudden deaths (Committee on Safety of Medicines, 1999). Thioridazine, which has often been implicated in sudden cardiac death or cardiac arrhythmias, also causes concentration-related QT interval prolongation (Hartigan-Go *et al*, 1996). Other psychotropic drugs that have this effect include tricyclic antidepressants and lithium (Thomas, 1994) and this may be particularly important when these drugs are used in combination with antipsychotics (Heiman, 1977). The repolarisation delay is a dose-related phenomenon and is therefore particularly common after drug overdose, with high-dose therapy and in the presence of drug interactions or diseases that delay the elimination of these agents.

There have been few systematic studies to determine the frequency of ECG

abnormalities in patients taking antipsychotic drugs. Early research suggested that such abnormalities, including T wave changes, are present in 25-50% of those receiving phenothiazines, ECG changes being more common with thioridazine than chlorpromazine (Ban & St-Jean, 1965; Alvarez-Mena & Frank, 1973). The prevalence of T wave changes appears to increase with the dose of antipsychotic drug (Axelsson & Apstenstrom, 1982). These studies did not measure QT intervals but more recent research suggests that the QTc interval is prolonged in only a small proportion of patients. For example, in a recent study of 268 mixed psychiatric patients, 6% had a QTc interval above a widely accepted upper limit of 440 ms. No patients were found with a QTc interval of more than 500 ms, a threshold below which *torsade de pointes* is unlikely. The QTc prolongation was more prevalent in female and older patients and in those receiving thioridazine, and the latter effect was independent of age (Reilly *et al*, 2000). This finding is consistent with the apparently greater toxicity of thioridazine than other antipsychotic drugs when taken in overdose (Buckley *et al*, 1995). A study in Finland has suggested that a disproportionate number of sudden deaths are in psychiatric patients taking this drug (Mehtonen *et al*, 1991).

### NON-DRUG RISK FACTORS

Little specific evidence exists on the patient factors that might predispose to cardiac arrhythmias in the presence of antipsychotic drugs, but these are likely to be the same as those found with quinidine. The presence of underlying cardiac disease is particularly important. Some patients have QTc prolongation in the absence of drug treatment, either because of acquired cardiac disease or as a hereditary phenomenon, and are at particular risk. Other likely risk factors are previous arrhythmias, impaired left ventricular function, concurrent digoxin therapy and hypokalaemia from any cause, including diuretic treatment (Nguyen *et al*, 1986; Minardo *et al*, 1988; Slater *et al*, 1988; Pratt *et al*, 1989).

Important questions about sudden death in psychiatric patients therefore remain. What is the contribution of underlying physical illness? What part is played by misuse of illicit drugs, and by alcohol and tobacco? Do restraint and

physiological arousal increase risk? Even the number of cases is unknown. Then there is the central issue of the role of anti-psychotic drugs. Are they, after all, a cause of sudden death? If so, which drugs are responsible? Is risk linked to high dosage or polypharmacy?

## NEW STUDY

The new study, funded by the Department of Health, aims to answer these questions and to make recommendations for clinical practice. It is firstly a survey of the clinical circumstances in which sudden unexplained deaths occur in psychiatric in-patients. This part of the study is analogous to the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness (Appleby *et al*, 1997), and the three collaborating centres are Manchester (where the Inquiry is based), Newcastle-upon-Tyne and Cardiff. Secondly, it is a case-control study from which risk factors can be identified and their impact quantified. The controls are matched in-patients who were alive at the time of death of the corresponding case.

Both cases and controls will be taken from the National Health Service contract data-set on hospital in-patients, to which all hospital trusts contribute. The initial sample of potential cases will consist of everyone who has died as a psychiatric in-patient. The research team will write to the responsible consultant, asking him or her to complete a questionnaire about the patient. The first section of the questionnaire determines whether the patient's death satisfies a definition of sudden unexplained death; if it does, there are further sections to complete on, in particular, clinical history and treatment. The controls are selected randomly from in-patients nationally, so it is unlikely that both case and control will come from the same hospital – otherwise hospital policies on care and treatment could make it hard to find differences. The questionnaire for controls is the same as for cases. An important feature of the study is that the research team will not know the identity of either cases or controls; they will be known only by their hospital numbers.

The expected frequency of sudden unexplained death is such that few psychiatrists will be asked to complete more than

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one questionnaire. Most will not be asked at all. The response rate in the National Confidential Inquiry is 92% (Appleby *et al*, 1999). The success of the new study will similarly depend on the cooperation of busy clinicians; a similar response will help us address one of the most sensitive questions facing clinical practice.

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