

# Council Report

## **The association between antipsychotic drugs and sudden death** CR57. 1997. 51 pp. £7.50

In 1993 the Royal College of Psychiatrists published a consensus statement on 'The Use of High-Dose Antipsychotic Medication' (Thompson, 1994). One of the main recommendations made in this report was that "the lack of clear information about sudden, unexplained deaths in psychiatric hospitals and the unease surrounding them suggests that consideration should be given to establishing a study under the auspices of the Psychopharmacology Group of the College".

In 1994, a Working Group of the Psychopharmacology Sub-Committee was established to investigate the association between antipsychotic drugs and sudden death. The relevant published literature was reviewed to determine what was currently known about the nature and extent of the problem, and possible mechanisms. An epidemiologist joined the Working Group to advise on epidemiological issues, and draft versions of the report were circulated for comment to people with relevant expertise in clinical psychiatry, cardiology, clinical pharmacology and sudden death. The final report was approved by Council on 29 January 1997.

The Working Group agreed to use the following working definition of sudden, unexplained death, which is based on the published literature: "Sudden, unexpected, unexplained death can be defined as death within one hour of symptoms (excluding suicide, homicide, and accident) (Ungvari, 1980) which is both unexpected in relation to the degree of disability before death (Kuller *et al*, 1967) and unexplained because clinical investigation and autopsy failed to identify any plausible cause (Hirsch & Martin, 1971)."

### *Sudden, unexpected death*

Since the 1960s, there have been regular reports of sudden, unexpected death in people receiving antipsychotic medication. Further, the Committee on the Safety of Medicines has received reports of cases of unexplained sudden death and fatal cardiac arrest/arrhythmias in people receiving various antipsychotic agents. The data available covered the period since each drug was introduced into clinical practice, up to May 1996. These reports need to be seen against the background estimate that between

15 and 30% of all natural fatalities in the developed world occur suddenly and unexpectedly (Kannel *et al*, 1975; Gullestad & Kjekshus, 1992). An official investigation, similar to the College's, was commissioned by the American Psychiatric Association. This review of the published evidence does not provide sufficient data to prove that sudden death is more likely among people being treated with antipsychotic medication compared to the general population (Simpson *et al*, 1987).

Nevertheless, there is increased risk of mortality for people with schizophrenia, much of which is due to suicide (Tsuang & Woolson, 1978; Black & Fisher, 1992). Research suggests that factors such as smoking, poor nutrition, poor environmental conditions and lack of adequate medical and social care may contribute to the excess mortality related to cardiovascular and respiratory disease in people with schizophrenia (Jenkins, 1990).

However, there are also concerns that cardiovascular toxicity related to antipsychotic drugs may be a contributory factor.

### *Antipsychotic medication*

Antipsychotic medication is the mainstay of treatment for schizophrenia. None of the available agents is free from the risk of adverse effects, and all produce side-effects. These include extrapyramidal symptoms, hypotension, sedation and weight gain. Further abnormalities of the electrocardiogram (ECG) are relatively common in people receiving neuroleptics, occurring in around 25% of cases (Thomas, 1994). These ECG changes have generally been considered benign. Prolongation of the QT interval (which represents the combined duration of the action potential and the subsequent ventricular repolarisation phase) is relatively common. Interest has focused on this abnormality on the basis that it may rarely lead on to more serious ventricular arrhythmias. However, there is no consensus on the clinical significance of a prolonged QT interval related to the administration of antipsychotic treatment. Arrhythmias are rare, and other factors may be required to trigger an arrhythmia in the presence of QT interval prolongation (Zehender *et al*, 1991), such as coincident cardiac disease, prescribed and illicit drugs that can also affect the QT interval or have other cardiotoxic effects, stress or extremes of emotion or physical exercise.

Stress and strenuous exercise are both related to sudden death in the non-psychiatric population (Spitz, 1985; O'Hallaran & Lewman, 1993) and both are likely to be relevant in cases where a patient is being physically restrained. The vigorous activity of a disturbed patient being restrained creates a situation comparable with that seen with sudden death in sport (Wright & Salem, 1995) or the fatal collapse of young soldiers during physically demanding exercises. The key questions still to be addressed are whether the effects of standard doses of antipsychotic medication might interact with such states of physiological arousal and exertion to further increase the risk of serious cardiac arrhythmias, and if so, what would be the relevant mechanism. At present, the possible contribution of antipsychotic drug treatment to a death in such a situation is often difficult if not impossible to assess (Laposata *et al.*, 1988).

The potential risks of antipsychotic medication must be weighed against their undoubted benefits in the treatment of acute psychosis and the prevention of relapse in schizophrenia. People with serious psychiatric illness may require such medication for long periods, if not throughout their lives, in order to be able to function effectively in society and minimise the disadvantages of their illness. The relationship between therapeutic benefit and serious toxicity can be expressed in terms of a therapeutic index, which is wide for antipsychotic agents compared with some other commonly-prescribed psychotropic drugs, such as lithium or tricyclic antidepressants. Thus, these drugs have been perceived as relatively safe, although such a view has not generally taken into account differences between the various antipsychotic agents.

Lastly, the Working Party reviewed the management of patients with asymptomatic prolongation of the QT interval on the ECG who require antipsychotic medication, and briefly examined the implications and utility of monitoring blood levels of antipsychotic drugs in clinical practice.

#### *Clinical management*

Given the uncertainty regarding the mechanisms underlying sudden death in psychiatric patients receiving antipsychotic medication, and a lack of any systematic data relevant to an individual patient's risk, or the relative risk of various antipsychotics, the Working Group provides some suggestions regarding the judicious prescribing of antipsychotic medication in the following clinical situations: in general use; for acute sedation; when considering a trial of high dose treatment; treating elderly patients; the administration of antipsychotic drugs in combination with other antipsychotics and/or other psychotropic medication.

#### *Summary*

Currently, there are insufficient epidemiological data to prove that sudden death is more likely among people being treated with antipsychotics than it is among the general population. Equally, there are no data to prove that there is no causal relationship between the use of such medication and sudden death. The possible mechanisms that may underlie such a relationship remain an area for conjecture and hypothesis.

#### *Recommendations*

The members of the Working Party call for further epidemiological evidence to be gathered to determine the incidence of sudden death in people treated with antipsychotic medication, and for the relevant pharmacological and physiological mechanisms to be clarified.

The Working Group strongly recommends that a systematic investigation of sudden death in psychiatric patients receiving antipsychotic drugs is undertaken by the Confidential Inquiry into Homicides and Suicides. A further suggestion is for a case control study to identify and estimate the relative contribution of the putative factors relevant to sudden death among patients treated with antipsychotic medication.

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