Antipsychotics and sudden death: is thioridazine the only bad actor?†

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For at least the past 30 years it has been known that people with schizophrenia have higher death rates, particularly from cardiovascular causes, than would be expected on the basis of demographics (Allebeck & Wistedt, 1986; Mortensen & Juel, 1990; Newman & Bland, 1991; Walker *et al*, 1997). Initially, suspicion focused upon lifestyle factors, such as ubiquitous smoking and poor self-care, and perhaps upon a direct effect of the disease. However, some of the suspicion began to shift to the drugs used to treat the disease, fuelled both by the accumulation of case reports among antipsychotic users of serious ventricular arrhythmias and sudden unexpected deaths (Liberatore & Robinson, 1984; Kriwisky *et al*, 1990; Mehtonen *et al*, 1991; Donatini *et al*, 1992; Thomas, 1994; Jackson *et al*, 1997; Ravin & Levenson, 1997; Zarate *et al*, 1997; Dickinson, 2000), as well as advancing understanding of the electrophysiological properties of these drugs (Thomas, 1994; Suessbrich *et al*, 1997; Drici *et al*, 1998; Rampe *et al*, 1998; Shader & Greenblatt, 1998; Studenik *et al*, 1998; Reilly *et al*, 2000).

THIORIDAZINE AND SUDDEN DEATH

Some of the evidence suggested that thioridazine, at one time one of the most commonly used medications for major mental disorders, might pose particularly elevated risk. Thioridazine has pronounced effects on K^+ channels and materially prolongs the QTc interval (Thomas, 1994; Reilly *et al*, 2000), effects that in other medications have reliably been associated with increased risk of torsades de pointes. Numerous case reports also linked this agent with increased risk of sudden unexpected deaths (Liberatore & Robinson, 1984; Donatini *et al*, 1992). These data have led regulatory authorities to change the labelling of thioridazine to discourage use of this agent unless other antipsychotics are not efficacious (Zarate, 2001).

In the present issue of the *Journal*, the findings of a comprehensive and careful investigation appear to support this view (Reilly *et al*, 2002). In a review of all deaths occurring in 5 in-patient facilities over a 12-year period, 69 probable sudden unexplained deaths were identified and matched with appropriate controls. Using the criterion of statistical significance ($P<0.05$), only thioridazine was linked with an increased risk of sudden death.

This finding would be particularly convenient for those who treat patients with schizophrenia and other major mental disorders, for which antipsychotics are the therapeutic mainstay. With the availability of several atypical antipsychotics, there is now very limited justification – based upon efficacy and side-effects – for the use of thioridazine. Although older agents will occasionally be used, these will primarily be for patients who do not respond to the atypical antipsychotics or for whom depot preparations are required.

OTHER ANTIPSYCHOTICS

Unfortunately, several lines of evidence suggest that the story is not so neat. The literature suggests that all currently available antipsychotics have electrophysiological properties that should increase the risk of sudden cardiac death (Zarate, 2001). There are case reports of torsade de pointes and sudden deaths for most of these. Indeed, clusters of sudden deaths have kept some promising novel agents off the market and have delayed the licensing of others (Zarate, 2001). Some epidemiological studies now provide evidence that several of the typical antipsychotics increase the risk of sudden cardiac death (Ray *et al*, 2001). The present study, an impressive achievement, nevertheless did not have sufficient power to demonstrate in a head-to-head comparison that thioridazine was associated with greater risk than the other specific drugs: the upper bounds of the 95% confidence intervals for these were all above 4. Furthermore, because of the time period of the study, the investigators could not study the effects of the atypical agents.

CLINICAL IMPLICATIONS

Thus, until there is substantially more evidence, it would be prudent to assume that all available antipsychotics have the potential to increase the risk of serious ventricular arrhythmias and thus sudden cardiac death. Further work is urgently needed to better define the absolute risk – a better guide to clinical decision-making than odds ratios or relative risk (Sackett *et al*, 1991), particularly for the atypical agents which are now widely used. Although defining this risk more accurately would not lead to withholding the substantial benefits of antipsychotics from patients with major mental illness, it may lead to more appropriate use of these agents in patients for whom the use of antipsychotics provides marginal benefits or who already have cardiovascular disease.

DECLARATION OF INTEREST

None.

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