Review Article

Antipsychotic Drugs and Sudden Death

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Abstract

Sudden, unexpected death may occur in apparently healthy individuals. Its occurrence in psychiatric patients has raised the concern that the use of psychotropics, especially antipsychotics, may be associated with an increased risk of sudden death. This concern is maintained even though not all psychiatric patients who have succumbed to sudden death have been on psychotropics. Early reports presented the concern that the use of chlorpromazine and thioridazine were associated with sudden death. More recently, the focus shifted to the more potent agents. Indeed, the FDA Advisory Committee discussed the possibility of a connection between sudden death and haloperidol. No decision could be reached by the FDA Committee because of the enormous complexity of the problem. Nonetheless, since sudden death continues to catastrophically complicate the course of some patients, the scope of this review is to further investigate the relationship between antipsychotic agents and sudden death.

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There is widespread, serious concern about the hazards of psychotropic medication, particularly sudden death with high doses of antipsychotic (narcoleptic) drugs. This concern follows several reports of unexpected deaths in young people, usually males, where the concurrent prescription of antipsychotic drugs has been implicated. The public perception is that these deaths occur when the medication is used in high dosage in disturbed patients. There is some suspicion of an ethnic bias, with young men of Afro-Caribbean origin being more commonly involved, although no data exist to substantiate this. The death rate among psychiatric patients tends to be higher than that of the general population, but suicide and accidental deaths may account for much of this excess.[1,2] Sudden, unexpected death is perhaps more common in the general population than might be expected. It has been estimated that between 15–30% of all natural fatalities in the industrially developed world occur suddenly and unexpectedly.[3,4] Davies has suggested that there are 50–100 sudden deaths in Britain every year that could be categorized as due to the sudden adult death syndrome, and for which there is no specific explanation.[5,6] Nevertheless, it would seem that the cardiovascular mortality of patients with chronic schizophrenia exceeds that of the general population[7] and the cardiovascular toxicity of neuroleptics may be a contributory factor.

Antipsychotic (neuroleptic) drugs have generally been

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regarded as a group of drugs with a good margin of safety, but there have been regular case reports of sudden death associated with these agents since the 1960s. Committee on Safety of Medicines have received reports of 31 cases of unexplained sudden death and 63 reports of fatal cardiac arrest/arrhythmias in association with people treated with various antipsychotic drugs, covering the period that each drug was introduced up to May 1996. The role played by antipsychotic drugs is often uncertain, but when sudden death occurs in previously healthy, young individuals a common conjecture is that medication played a part. It is essential that epidemiological evidence is gathered to determine the extent of this problem, and that the relevant pharmacological and physiological mechanisms are clarified. This is a key task, and has yet to be undertaken.

The first step in such an investigation would be to agree a definition of sudden death. Brown & Kocsis (1984) referred to "death occurs instantaneously or within 24 hours of the onset of acute illness", excluding death by suicide, homicide or accident.[7] The following definition is taken from Jusic & Lader (1994): Sudden, unexpected, unexplained death can be defined as death within one hour of symptoms[8] (excluding suicide, homicide and accident)[9] which is both unexpected in relation to the degree of disability before death[10] and unexplained because clinical investigation and autopsy failed to identify any plausible cause.[11]

Schizophrenia

Schizophrenia is a relatively uncommon disease in the general population with prevalence between 1.4–4.6 per 1000 population at risk, an incidence rate for new cases in the range of 0.2–0.4 per 1000, and a morbid lifetime risk around 1% (12-14). It varies in its severity and its clinical course. Although the illness represents a major part of the workload of specialist psychiatric in-patient and out-patient practice, its management is not confined to psychiatrists. Many affected patients are treated exclusively in general practice while others are stabilized in specialist practice before being returned to their general practice for long-term follow-up and care. It is thought that a substantial proportion of the vagrant population is affected with schizophrenia-like illnesses. Among this subgroup the disease may be seen in its more florid form because of the lack of treatment. The main treatment is antipsychotic medication. The duration of treatment varies between patients, as does the dose that is required for control of the symptoms. None of the drugs currently available is free from the risk of adverse effects, all produce side-effects. The principal side-effects include extra pyramidal symptoms (Parkinsonism, akathisia, dystonia and tardive dyskinesia), hypotension, and interference with the temperature regulating system, the so-called neuroleptic malignant syndrome, and a number of idiosyncratic effects on the cardiac system.

Some of the side-effects and adverse effects are dose-related. Interactions between antipsychotics and other medication have been documented. For example, the concurrent use of phenothiazines and tricyclic antidepressants can result in a rise in the blood levels of the two drugs with a consequent increase in the risk of dose-related side-effects of both.[12,15]

Cardiac effects of antipsychotic drugs

Abnormalities of the electrocardiogram (ECG) are relatively common in people receiving neuroleptics, occurring in around 25%.[16,18] There are numerous reports of ventricular arrhythmias associated with repolarisation disturbances such as prolonged QT intervals, widening of QRS complexes, depression of ST segments and most commonly abnormal T-morphology or large U-waves.[19-27] They are observed more often in patients with pre-existing heart disease.[28] The phenothiazine group of antipsychotics display electrophysiological properties like those of the class IA antiarrhythmic agents (quinidine-like), involving blockade of potassium and sodium channels, leading to a prolonged duration of the action potential (which also slows conduction), refractory period and QT interval. However, members of other antipsychotic classes such as haloperidol and droperidol, butyrophenones,[29-31] pimozide, a diphenylb utylpiperidine,[32] and sultopride, a substituted benzamide,[33] have also been reported to cause QT prolongation. Warner et al (1996) found that QTc (QT interval corrected for heart rate) prolongation (>420 ms) was significantly more common (23%) in a sample of 111 chronic in-patients with schizophrenia receiving antipsychotic medication than in 42 age-matched, drug-free controls (2%).[34] QTc prolongation was also significantly more likely in those patients receiving mega doses, that is, above 2000 mg chlorpromazine equivalents a day. A new antipsychotic drug, sertindole, introduced in July 1996, can also cause prolongation of the QT interval. The prescribing information for the drug states that it is contraindicated in patients with prolongation of the QT interval and that all patients should have an ECG performed before the drug is started and Thensubsequently at regular intervals. According to a report in the Lancet,[35] there was disagreement over the safety of sertindole at the meeting of the Food and Drug Administration advisory committee at which the drug was approved. These ECG changes have commonly been considered benign, and even now there is no consensus on the clinical significance of prolonged QTc.[36] However, QT prolongation with other compounds has been shown to produce serious arrhythmias that have sometimes proved fatal. Drug-induced QTc prolongation may be important even if the mean increase is not very large. For example, the drug terodiline was withdrawn after causing QT prolongation, torsade de pointes, and sudden death. In healthy volunteers, therapeutic plasma concentrations are associated with increases in mean QTc of only 23 ms, which are similar to the increases associated with quinidine and prenylamine. Nevertheless, much larger increases occurred in a minority

of patients who developed arrhythmias. These included those predisposed by existing problems such as heart disease and congenital repolarisation abnormalities. Thus, apparently benign QT prolongation in one subject may indicate that another more susceptible patient might develop extreme QT prolongation and arrhythmias with the same drug at the same dose.

Furthermore, small increases in QT interval may increase the risk of VT/ torsade de pointes. Although the increased risk is probably small, because minor QT prolongation is common the risk is applied over a large population. The number of excess cases of sudden death in the large numbers of patients with minor QT prolongation may exceed those in the small numbers of patients with extreme QT prolongation. In his review of drug-induced QT prolongation, Thomas (1994) was of the opinion that neuroleptic drugs presented a particular hazard in terms of provoking dysrhythmias (proarrhythmia) as they are commonly prescribed "in high doses and in combination", by psychiatrists who have little training in detecting such problems. A lack of ECG facilities and interpretation

May be particular problems.[36]. Thioridazine, and less frequently, chlorpromazine, have been particularly implicated in the development of ventricular tachycardia, primarily in patients taking overdoses.[8]

For example, Buckley et al (1995) investigated the clinical andelectrocardiographic features associated with neuroleptic poisoning and compared thioridazine with other neuroleptics.[37] of 299 consecutive patients admitted with neuroleptic poisoning, the mostcommonly ingested drug was thioridazine (104 patients). The other antipsychotics taken were chlorpromazine,[19] trifluoperazine,[36] pericyazin35, haloperidol,[33] prochlorperazine, [18] fluphenazine,[8] or other neuroleptics.[7] Sixteen patients who had ingested more than one neuroleptic were excluded from comparative analysis. After taking into account variables such as for age, sex, dose ingested and co-ingestion of tricyclic antidepressants or lithium, thioridazine was still found to be significantly more likely to cause tachycardia, a prolonged QT interval, prolonged QTc (> 450 ms), a widened QRS (> 100 ms) and arrhythmias. Fulop et al (1987) noted that ECG abnormalities had been found in 10% of patients treated with pimozide, leading to recommendations in the USA and UK for periodic ECGs in patients receiving this drug.[38] They commented that the abnormalities included prolongation of the QTc interval which increases the risk of a potentially fatal arrhythmia. From 1971 to 1995, the Committee on Safety of Medicines received 40 reports (16 fatal) of serious cardiac reactions, predominantly arrhythmias, with pimozide.[39] The recommendations to doctors included an annual ECG for patients receiving the drug, and if the QT interval were prolonged, review of whether to withdraw the treatment and continue under close supervision. Torsade de pointes is a particular cardiac problem related to antipsychotic medication that has been implicated as a possible cause of sudden death, in those individuals with a past history of disturbances of cardiac rhythm or other cardiac symptoms. This arrhythmia is a variant of paroxysmal ventricular tachycardia associated with a prolonged QT interval or prominent U waves on the ECG.[40-43] although torsade de pointes may remit spontane ously, it is potentially lethal in that it can progress to ventricular fibrillation.[44] Torsade de pointes may be asymptomatic or cause self-limiting palpitations, while a minority of episodes may precipitate sudden death. This arrhythmia has been reported in association with antipsychotic drugs, specifically haloperidol[45-50] and thioridazine.[40,51]

How do drugs lengthen the QT interval and produce ventricular arrhythmias?

The QT interval represents the combined duration of the action potential and the subsequent ventricular repolarisation phase. The action potential is caused by fast-activating and inactivating sodium and calcium currents. Its length is largely determined by an ensuing plateau phase. Repolarisation occurs when the net outward current becomes dominant. This current is regulated by potassium efflux and influx through six or more different channels. of these, three are dominant, iK1, iK, and iT0. The basal potassium current is determined by iK1, which is blocked by inorganic ions including magnesium, and quinidine, and modulated by vagal activity. The delayed rectifier current, iK, is modulated by beta receptor occupancy, stimulation of adenylate cyclase, and production of cAMP. IK and iT0-like currents are the target of most known Class III antiarrhythmic agents, such as amiodarone. Although our understanding of the electrophysiological effects of antipsychotics is incomplete, it seems that, in addition to general membrane stabilizing properties, antipsychotic drugs and their metabolites may have selective and differing effects on the ion channels which govern length of the QT interval. For example, thioridazine has been shown to decrease the velocity of the action potential upstroke without altering the resting potential, whereas chlorpromazine has a greater effect on the resting potential.[52] One important prediction from this is that drugs would differ in their propensity to cause arrhythmias, although no comparative studies have yet been done. Whether a drug-induced QT prolongation results in an arrhythmia depends on the presence of one or both of the following.[31]

Increased cellular excitability. Early after-depolarisations are associated with abnormal repolarisation and interrupt the repolarisation process. Torsade de pointes characteristically interrupt terminal repolarisation of a markedly prolonged QT interval, especially in the presence ofbradycardia.[52]

Abnormal dispersion of prolonged ventricular repolarisation.

This would favour a re-entrant mechanism, as different parts of the ventricle remain refractory for differing periods.[53] slow conduction also favours re-entry. Cardiac risk factors

for torsade de pointes may also include frequent ventricular ectopics which may trigger the phenomenon by landing on a T wave. Also, QT dispersion is much larger after a ventricular premature contraction and this may increase the risk.

What other factors interact with drug-induced QT interval prolongation to increase the risk of sudden death?

Although QT interval prolongation is common, proarrhythmic events are rare, and death is rarer still.[52] this seems in part to be because one or more additional cofactors may be required to trigger an arrhythmia in the pres ence of QT interval prolongation. These cofactors may be grouped as follows.

Cardiac

Congenital long QT syndromes (LQTS), such as Romano Ward, Jervell and LangeNielsen, ischaemic heart disease, myocarditis, sinus bradycardia <60 beats perminute.[52]

Other drugs

Additively, by directly lengthening the QT interval, or indirectly, by altering the metabolism of drugs which directly lengthen

The QT interval.[54] Drugs may also affect the risk of torsade de pointes by changing heart rate, as risks are higher at slower rates, or by altering sensitivity to catecholamines.

Metabolic

Hypokalaemia, hypomagnesaemia, hypocalc-emia, hypothermia. Causes of autonomic instability Stress and extremes of emotion,[55] extremes of physical exertion, sudden shocks.[56]

Other cardiac mechanisms for sudden death

It has also been suggested that antipsychotic drugs may be responsible for atoxic cardiomyopathy, leading to death by ventricular fibrillation or cardiac arrest. Ultrastructural damage to the heart associated with circulating auto-antibodies, especially those to skeletal muscle, heart, DNA, mitochondria and smooth muscle, has been found in patients who have died from drug-related, fatal arrhythmias.[57] Further, clozapine has been associated with myocarditis which has been found in cases of sudden death.[58-60]

Conclusion

From a neurocardiologic perspective, antipsychotic drugs have the potential for both increasing and decreasing the risk of sudden death.[61] This notion that drugs with electrophysiological properties similar to quinidine are as likely to reduce as to increase the risk of arrhythmias must be viewed with some circumspection. Simpson et al go on to state that "Ultimate outcome is probably determined by a multitude of interacting factors, and the role played by the drug in a given individual is difficult, if not impossible, to determine.[61] Where there is limited information, the tendency to cite neuroleptics as the cause of death in cases of sudden death with negative findings at postmortem should be resisted, according to Laposata et al (1988). Otherwise, efforts to identify the correct cause of death in such cases, and clearly establish the risk of neuroleptic treatment, will be hindered.[62]

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