Sudden Death in Psychiatric Patients

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Psychiatric patients and apparently normal individuals have died suddenly for reasons that remain unexplained despite postmortem examination. The phenomenon of sudden death in psychiatric patients was observed both before and after the discovery of psychotropic drugs. However, malpractice suits filed after the discovery of antipsychotic drugs often attribute the cause of death of psychiatric patients to these drugs. This article will review the literature on sudden death in psychiatric patients, particularly case reports in the English literature of 1957 to 1980 and our experience in the Shanghai Psychiatric Hospital, in order to examine the possible role played by antipsychotic drugs. The epidemiology of sudden death, the cardiovascular effects of antipsychotic drugs, and other possible causes of sudden death such as exercise or stress will be examined.

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CRITICAL REVIEW OF CASE REPORTS OF SUDDEN DEATH

There have been reports of sudden, unexpected, and unexplained deaths among psychiatric patients, most of whom were receiving psychotropic drugs. Examining the literature, we found that many cases would not meet the definition of sudden, unexpected, and unexplained death. Some of these patients had preexisting life-threatening diseases, and their deaths were expected and readily explainable. Many had positive autopsy findings such as myocardial infarction, asphyxia or aspiration, pulmonary embolus, intestinal obstruction, or paralytic ileus which explained the death. We performed a critical review from literature using the following criteria for sudden death: 1) the death was discovered less than 24 hours after the patient was last seen alive; 2) the patient had been physically healthy, had had no preexisting life-threatening illnesses; 3) the patient had received usual dosages of psychotropic drugs; 4) the result of the autopsy was negative, yielding no findings which explained the cause of death; and 5) patient data was relatively complete and available for analysis.

In the English literature (1957 to 1980), we found only 35 cases (21 males and 14 females) that met our criteria of sudden, unexpected, and unexplained death. Their average age at time of death was 40 (range 20 to 70 years), and most (80%) were in the group of 25 to 54 years. Sixteen patients (45.7%) were taking chlorpromazine alone at the time of death.
four (11.4%) thioridazine, three (8.6%) trifluoperazine; two (5.7%) prochlorperazine, and one (2.9%) each perphenazine, fluphenazine, haloperidol, carperazine, and levomepromazine. Five patients (14.3%) were taking two or more psychotropic drugs: two chlorpromazine and thioridazine, one trifluoperazine and fluphenazine, one chlorpromazine and trifluoperazine and haloperidol, and one thioridazine combined with imipramine and desipramine. The frequency of the drugs was roughly similar to their use in psychiatric patients at that time, with chlorpromazine being the most frequent antipsychotic in use. Few haloperidol-associated deaths were reported in the earlier papers, but they have become more frequent in recent articles. Thioridazine was involved in seven cases (20%): four cases alone and three cases combined.

As to the circumstances of death, 20 (57%) were described as found dead, eight (22.8%) had some evidence of collapse, seven (20.0%) had convulsive seizure, and three (8.6%) had symptoms of breathing difficulty just before death, but all autopsies were nonspecific. The only exception was the case reported by Richardson, in which collections of mucopolysaccharide materials were found in the smaller arterioles of the subendocardial region of the heart. The clinical significance of such findings was unknown, and these findings have never been confirmed.

We made a survey of sudden death in the patients of the Shanghai Psychiatric Hospital. There were 31,960 patients admitted to this hospital from 1970 to 1979. Thirty-nine patients died suddenly during the treatment with psychotropic drugs. Among these 39, 18 were explained by pathological findings such as heart disease, asphyxia, infections, megacolon, etc. Only 21 cases might be classified as unexplained sudden death (one case per 1,522 patients). Neither the total mortality nor the mortality of unexplained, sudden death was markedly higher than the roughly estimated mortality of the general population. We made the preliminary version of our review available to the American Psychiatric Association Task Force on Sudden Death.3

**EPIDEMIOLOGICAL STUDIES OF SUDDEN DEATH**

Virtually all psychiatrically hospitalized patients are treated with psychotropic drugs. Because the number of reported sudden deaths in psychiatric patients has been relatively small in relation to the tremendous numbers of patients receiving psychotropic drugs, the possibility of accidental coincidence needs to be examined. Unexpected, natural sudden death is a common phenomenon in normal populations. Approximately 400,000 persons in the United States die suddenly each year.1,2 This is about one death per minute in the United States. In some cases, postmortem examination can elucidate the cause of death, but often the postmortem examination is negative.

In 20% of the cases of sudden cardiac death, no evidence of ischemic necrosis of myocardium was found in histochemical and biochemical studies. We assumed that death resulted from a fatal arrhythmia. Since sudden, unexplained death, presumably caused by a fatal arrhythmia, can occur in psychiatrically normal persons, we expect that such deaths would also occur in psychiatric patients.

It is possible that the causes of sudden death in psychiatric patients are only coincidentally related to their psychotropic medication and are caused by the same pathophasiologic events that afflict the general populace. If antipsychotic drugs in fact cause sudden death, the incidence of sudden death should be higher in psychiatric inpatients than in the general population, and the incidence of sudden death should also have increased after the introduction of the antipsychotics. Therefore, do the psychiatric patients receiving antipsychotic drugs have a high mortality rate compared with the general population? Richardson7 estimated that there might be one or two cases of unexpected sudden death in a 2,000-bed psychiatric institute, but this mortality may not necessarily be significantly higher than that of a normal population. Swett and Shader9 conducted a prospective study at Massachusetts Medical Center where they monitored a random sample of 1,832 consecutively admitted psychiatric patients. They found two sudden deaths in this group, but neither of the two deaths were attributed to tricyclic antidepressants or phenothiazines. Ungarri8 studied 11,935 patients treated with antipsychotic drugs at the Department of Psychiatry, University of Budapest, over a period of 11 years from 1968 to 1978, and found eight who died suddenly and unexpectedly. This mortality rate (one case per 1,492 patients) was not higher than that of the general population at that time, which was one per 1,458 inhabitants in Budapest. Note the similarity of the prevalence of sudden death in the Shanghai Psychiatric Institute and the Budapest Mental Hospital.

Comparing the incidence of sudden death in psychiatric patients before and after the introduction of psychotropic drugs may uncover a possible causal link between sudden death and psychotropic drugs. Prior to the discovery of antipsychotic drugs, sudden death was reported in severely disturbed psychiatric patients often after days, weeks, or months of agitation. While many of the early sudden deaths were seen in agitated patients, some did not exhibit hyperactivity.13 In an analysis of hospital statistical data comparing the death rate just before and just after the introduction of antipsychotics, Brill and Patton failed to find an increase of death associated with the use of antipsychotic drugs.14 Craig and Lin4 compared the age-adjusted death rate of psychiatric inpatients and the general population before the introduction of psychotropic drugs in Norway and Michigan and after the introduction of psychotropic drugs in New York.
state. They constructed a ratio of inpatient death rate to general population death rate. If antipsychotic drugs increase the death rate, we would expect the ratio to be higher after the introduction of antipsychotic drugs, but the opposite is true.

In brief, the epidemiological data do not show an increase of sudden death in patients treated with antipsychotic drugs. Because sudden death is common in the general population and almost all psychiatric patients are on medication, it is possible that the medication does not play a great role in sudden death and its association with sudden death is coincidental.15

MECHANISM OF SUDDEN DEATH

- Antipsychotic Drugs and the Heart

If the antipsychotic drugs do in fact cause sudden death, can we identify the mechanisms responsible? Since the mechanism of sudden death is presumably an arrhythmia, do the antipsychotics produce EKG changes suggesting that they would produce fatal arrhythmias? The effect of antipsychotic drugs on the heart has not been well studied with modern techniques. The tricyclic antidepressants (TCA) have been found to have quinidine-like properties.35 Hence, the TCAs would be beneficial to patients for whom quinidine is indicated and the opposite when quinidine is contraindicated. Thioridazine and chlorpromazine might well have quinidine-like properties.36-46 Gremaldi and Maggi found that both chlorpromazine, which has quinidine properties, and haloperidol protect against CaCl₂ arrhythmias, with haloperidol possibly having a central effect because the authors note it does not have quinidine-like properties.40 What is lacking are studies of these drugs on the heart or cardiac diseases and disease-free humans.

It is always difficult to generalize from an unphysiologic concentration in a normal animal or animal model to the human. We note that levomepromazine has been used in post-acute myocardial infarction patients; its use is associated with a lower mortality than that in patients receiving pethidine. Haloperidol has also been used safely in high dose in this population. As early as 1953, Courvoisier and associates reported the ability of chlorpromazine to combat several types of cardiac arrhythmia.36 Aherwader and associates reported that a 30 year old female developed an arrhythmia with transient complete heart block, right bundle branch, and left anterior hemi-block as a result of chlorpromazine therapy.42 Withdrawal of the drug resulted in reversion to normal rhythm, while reintroduction caused similar rhythm disturbance to appear. Although not well studied, antipsychotics such as perphenazine, trifluoperazine, prochlorperazine, thioridazine and chlorprothixene may produce similar EKG change.3,15,43-46

The reports of serious arrhythmias with chlorpromazine use are rare. The few existing reports are complicated by the presence of concomitant severe systemic disease or the use of a multiple drug regimen. If the antipsychotics as a class were arrhythmogenic, we would expect a large literature of patients with antipsychotic induced rhythm disturbances which remit with drug discontinuance, but in fact, we could find no such literature.

- The Thioridazine EKG

Granauer and Murphy,43 Wendkos,15,40 and others44,45 reported studies in which patients receiving thioridazine produced electrocardiographic changes such as T-wave and ST segment changes. These changes are relatively nonspecific and occur in schizophrenics on placebo or in persons without known cardiac disease such as baseline or under stress.33,47-49 Thus the clinical significance of thioridazine changes, like other nonspecific EKG abnormalities, is uncertain.15,43,44 If the thioridazine EKG changes were responsible for sudden death, we would expect that most sudden deaths would have occurred with thioridazine, but in our survey the incidence of sudden death is not disproportionately higher in thioridazine-treated patients. Wendkos has reviewed this topic in detail and failed to find evidence implicating the typical thioridazine EKG effect as a cause of sudden death.15

Several cases of ventricular arrhythmia and severe heart block have occurred in association with the administration of thioridazine. Some of these arrhythmias have followed large dosages of these drugs. For example, Kelly reported that two patients who developed fatal ventricular tachycardia had received 1500 mg and 3600 mg of thioridazine per day.21 Giles reported a similar case, in which the patient died due to ventricular arrhythmia after receiving 3600 mg of thioridazine and 8 mg of perphenazine on the day of his death.50

The cardiac effects of antipsychotics are not well investigated, therefore, caution is required in speculation. This notwithstanding, it is quite possible that antipsychotics with quinidine-like properties (or other antiarrhythmic properties) could be beneficial to the hearts of patients in whom these properties are needed. By the same token, quinidine or any drug with similar properties, which could include thioridazine and possibly other neuroleptics, could be arrhythmogenic in patients with certain cardiac problems such as prolonged QT interval syndrome.51 For example, these drugs might contribute to producing Torsade de Pointes, a reentrant tachyarrhythmia associated with prolonged QT interval and initiated by a "late" premature ventricular contraction occurring on the prolonged T-U wave, and often progression to sustained ventricular tachycardia or ventricular fibrillation and cardiac arrest. Indeed, case reports of thioridazine-treated patients with Torsade de Pointes have been reported,52-57 but we would hasten to add that, to our knowledge, no case controlled studies have substantiated a causative relationship.

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The cause is known from clinical and autopsy data, but whether neuroleptics could predispose to such deaths is not known. Paralytic ileus is the result of the combined anticholinergic properties of the psychotropics prescribed and is a drug-explained death. Patients with seizure disorder are at slightly increased risk for sudden death, but when the seizure causes aspiration, the mechanism is explainable. Other than this, we have little to add except to note that the slight increase in sudden death in patients with seizure disorder is not well understood. Indeed, many of the same speculations have been made on the cause of this slight increase in mortality, such as linking cardiac arrhythmias to seizures. Although seizures do occur in schizophrenics, they are uncommon, hence, seizure could only explain a miniscule fraction of unexplained sudden deaths.

**AGITATION AND STRESS**

An acute psychotic episode is obviously stressful and is often associated with extreme agitation, necessitating seclusion or restraint, and, indeed, many episodes of sudden death occur in patients in seclusion or restraint. Therefore, could the agitation and stress of the psychotic episode be a causative factor in sudden death rather than the antipsychotic drug per se? Extreme psychomotor agitation may have the same effects as strenuous exercise.

One well-known example of sudden death with physical exhaustion is lethal catatonia. Lethal catatonia (synonymous with Bell’s mania or acute explosive mania) has been reported for more than 100 years and is characterized by: 1) persistent extreme psychomotor excitement, often with delusions or hallucinations; 2) a sudden, fatal outcome that usually follows the continual manic furor without any warning; and 3) post-mortem examination that never discovers any meaningful anatomical changes. This syndrome was not uncommon in the first half of this century before the introduction of psychotropic drugs. Peele and Loetzen located 65 such cases in a review of world literature. Derby reports 154 such cases in manic-depressives in one state hospital in a five-year period (1927-1932), before antipsychotic drugs were discovered and before ECT and insulin therapy were in widespread use in the United States. Exhaustion deaths are quite rare now, and it is quite possible that physical treatments have reduced the incidence substantially.

Sudden death also appears to be caused by strenuous exercise. It has sometimes happened in young athletes and healthy soldiers. Nineteen cases of sudden, unexpected cardiac death occurred in healthy, medically screened air force recruits (90% male, 17 to 28 years old) during a 42-day basic training period between 1965 and 1985. Strenuous exercise was associated with sudden death in 17 of 19 cases. Similarly, Koskeno found that sudden death was more common among conscripts in Finland than in other young men. Indeed, 33% of all non-violent death among conscripts was sudden death syndrome, and one third of all the cases occurred during near-maximum physical exertion. The incidence of sudden death in rugby players has been estimated to be about 1 per 50,000 rugby-hours and in the older referees about 1 per 3,000 rugby-refereeing hours. Obviously, since sudden death can occur in psychiatric patients, as in athletes, it is important that personnel be trained in CPR.

There is a large anecdotal literature from anthropology, including a now classic paper by Walton Cannon, on so-called voodoo death, where death is related to black magic or occurs at the height of religious ceremonies. In the American Psychiatric Association Task Force Report is a review of the literature, which supports that central nervous system events, either directly or mediated by the peripheral autonomic nervous system, can in animals or man contribute to arrhythmias or sudden death. Also, experimental stress can produce arrhythmias in man.
TABLE
Prevalence of Acute Psychological Stress Preceding Sudden Death

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Population</th>
<th>Time Frame*</th>
<th>Total No. of Cases</th>
<th>Number of Cases With Acute Stress</th>
<th>Prevalence of Acute Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myers &amp; Dewar</td>
<td>Postmortem</td>
<td>30 min</td>
<td>100</td>
<td>23</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 hrs</td>
<td>100</td>
<td>40</td>
<td>40%</td>
</tr>
<tr>
<td>Rissane et al</td>
<td>Postmortem</td>
<td>2 hrs</td>
<td>118</td>
<td>23</td>
<td>19%</td>
</tr>
<tr>
<td>Reich et al</td>
<td>Clinical</td>
<td>24 hrs</td>
<td>117</td>
<td>25</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Refers to period during which acute stresses occurred.

Furthermore, it has been shown that actual sudden death is preceded by acute psychological stress (Table).67-69 Engel collected histories of 170 sudden and rapid deaths during acute psychological stress.70 The epidemiology of sudden death shows the rates of sudden death for psychiatric patients and for the general population to be roughly equal. The data also failed to show an increase of sudden death in psychiatric patients after the introduction of antipsychotic drugs. There is no evidence that the antipsychotic drugs statistically produce dose-related fatal cardiac arrhythmias. Indeed, many of the antipsychotic drugs may exert an antiarrhythmic effect in ordinary doses, but research is lacking. If antipsychotic drugs are not the cause of ventricular arrhythmia and sudden death, then another mechanism must be at work. Good candidates would be acute stress and strenuous physical exercise accompanying the agitation of the psychotic episodes.

In this article, we have reviewed what little is known about sudden death in psychiatric patients. There is only one epidemiological study of sudden death per se,4 and even one more study might alter our knowledge considerably.

In the January 1968 issue of the New England Journal of Medicine, right ventricular cardiomyopathy was added to the growing list of disorders that can cause sudden death.72 These entities include myocarditis, congenital anomalies of the coronary arteries, sickle-cell trait, Q-T prolongation syndrome, and hypertrophic cardiomyopathy.

It is possible that the antipsychotic drugs could protect against, aggravate, or have no effect on other causes of sudden death. We need more information on the cardiac effects of antipsychotics and the diseases that produce sudden death in order to make any reasonable speculations. It is important to recognize that the causes of sudden death are not well worked out, and it is more accurate to say that we do not know, than to make up something speculative that may be false and misleading.

REFERENCES


