Comparative cardiac safety of low-dose thioridazine and low-dose haloperidol

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Aim

To compare the rate of ventricular arrhythmia, sudden death and unexplained or unattended death among users of thioridazine and haloperidol.

Methods

Observational cohort study of thioridazine and haloperidol users in the UK General Practice Research Database (GPRD) using data from 1987 through 29 June 2000. Patients were followed for 30 days following each study prescription. The event of interest was a diagnosis of ventricular arrhythmia, sudden death, or unexplained or unattended death. Cox regression was used to calculate rate ratios (RRs) and 95% confidence intervals (CIs), to examine potential confounding factors, and to examine dose-response relationships.

Results

Use of thioridazine and haloperidol in the GPRD was primarily in older patients, at low dose (median daily dose 31 mg thioridazine, 1.8 mg haloperidol). There was no association between thioridazine use and the rate of ventricular arrhythmia, sudden death, and unexplained or unattended death (adjusted RR 0.9, 95% CI 0.7, 1.1). The rate did not appear to increase with dose for either drug over the range observed.

Conclusions

These results suggest that low-dose thioridazine and haloperidol have similar cardiac safety.

Drug-induced sudden cardiac death and ventricular arrhythmia have arisen as major public health concerns in the past decade, resulting in the removal of more drugs from the market than any other adverse drug effect [1]. Prolongation of the electrocardiographic QT interval is widely used as an intermediate marker for a drug's ability to cause arrhythmias [2], although there is

growing recognition that the link between QT prolongation and the risk of clinical events is poorly understood [3].

Thioridazine is an antipsychotic drug that at doses of 300 mg day⁻¹ prolongs the Bazett-corrected QT interval more than haloperidol 15 mg day⁻¹ [4]. Cases of ventricular arrhythmia have been reported in temporal

association with both drugs [5, 6], although case reports are widely acknowledged to be of limited utility in inferring cause–effect relationships [7]. Reilly *et al.* studied hospitalized psychiatric patients and found that the odds ratio for sudden unexplained death associated with thioridazine was nine times as high as that of haloperidol. Ray *et al.* studied Medicaid outpatients and found that at doses >100 mg day⁻¹ of thioridazine or its equivalent, the rate of sudden cardiac death associated with thioridazine was 1.7 times as high as that for haloperidol [8]. In a previous study of Medicaid patients with schizophrenia, we found no overall difference in the rate of cardiac arrest and ventricular arrhythmia between thioridazine and haloperidol [rate ratio (RR) 0.9, 95% confidence interval (CI) 0.7, 1.2] [9]. However, those receiving more than 600 mg day⁻¹ of thioridazine had a higher risk than those receiving the equivalent haloperidol dose (RR 2.6, 95% CI 1.0, 6.6), and a dose–response relationship was evident for thioridazine, but not for haloperidol [9].

A well-known potential limitation of Medicaid studies is the possibility that results might not be generalizable to other populations [10]. Therefore, we sought to examine the generalizability of our findings in Medicaid by studying patients enrolled in a general practice medical record database from the UK.

Methods

Study setting

This study was performed using data from the UK General Practice Research Database (GPRD). The GPRD is the outpatient electronic medical record for approximately 3 million currently enrolled patients, and contains over 35 million patient-years of data. The database includes outpatient medications prescribed by the general practitioner (GP), outpatient diagnoses assigned by the GP, and hospital diagnoses that have been entered by the GP following receipt of a consultant's letter or discharge summary [11]. The GPRD has been used for over 200 published epidemiological studies. Associations with ventricular arrhythmia have been demonstrated in the GPRD for non-sedating antihistamines [12] and for a broad group of QT-prolonging drugs [13]. This study used data derived from the GPRD from its inception in 1987 through 29 June 2000.

Study design

We performed a cohort study of patients who received either thioridazine or haloperidol, and who had no prior recorded history of the study outcome, defined below. We had originally planned to restrict the study to individuals with a diagnosis of schizophrenia, as we had

done in our earlier study [9]. However, we discovered during the course of the study that only 9% of thioridazine users and 19% of haloperidol users had a schizophrenia diagnosis, and therefore eliminated this restriction, and instead examined schizophrenia as a potential confounder.

Exposure definition

We assumed that each prescription lasted for 30 days, which is consistent with the distribution of the calculated days' supply of thioridazine and haloperidol prescriptions (mode = 30 days) and with the distribution of the time between antipsychotic prescriptions (mode = 28 days). We also conducted secondary analyses assuming that prescriptions lasted 15 days and 45 days.

Outcome definitions and comparison with death records

The primary outcome was a composite endpoint consisting of diagnoses of ventricular arrhythmia, sudden death, unexplained death, and unattended death (Appendix). Subjects experiencing the outcome of interest did not contribute further observations.

We obtained anonymized 'Certified Copies of an Entry of Death' (CCEDs) for 171 outcomes that were followed by death within 2 days. We originally intended to validate our study outcome using these certificates. However, we learned during the course of the study that in the UK, cause of death information on CCEDs is entered by vital statistics registrars based on the registrar's interpretation of cause of death information recorded on the 'Certificate for Registration' of death, which is usually (but not always) completed by a physician. Because vital statistics registrars lack formal training in medical terminology, these certificates may not accurately reflect physician-assigned causes of death [14], which may themselves be less accurate than clinical diagnoses [15]. Therefore, rather than treating the CCED as a true gold standard for validating clinical diagnoses, we instead examined broad agreement based on whether the primary CCED cause of death was cardiac or noncardiac.

The primary CCED cause of death was of cardiac origin in 57% of those with a GPRD diagnosis of ventricular arrhythmia, and 58% in those with a GPRD diagnosis of sudden death, but only 26% of those with a GPRD diagnosis of unexplained or unattended death. Among those with a GPRD diagnosis of unexplained or unattended death, bronchopneumonia was the most common primary CCED cause of death. This suggested two possible explanations. The first is that bronchopneumonia is used as a 'default' cause of death in the absence

Table 1

Baseline characteristics of study subjects

Characteristic	Thioridazine (N = 63 640)	Haloperidol (N = 13 549)	Rate ratio (95% confidence interval) for association with ventricular arrhythmia, sudden death, unexplained death, and unattended death*
Female sex	40503 (64%)	7860 (58%)	1.6 (1.4, 2.0)
<i>Age, years</i>			
0–34	8901 (14%)	2281 (17%)	0.04 (0.02, 0.12)
35–44	6646 (10%)	1658 (12%)	0.14 (0.08, 0.24)
45–54	6203 (10%)	1710 (13%)	0.14 (0.08, 0.24)
55–64	5402 (8%)	1646 (12%)	0.30 (0.21, 0.45)
65–74	8048 (13%)	2083 (15%)	0.47 (0.36, 0.63)
> 75	28440 (45%)	4171 (31%)	1.0 (ref)
Current smoker	17454 (27%)	4157 (31%)	1.0 (0.7, 1.2)
<i>Diagnosis variables</i>			
Alcohol abuse	2970 (5%)	509 (4%)	1.3 (0.8, 2.1)
Asthma/chronic obstructive lung disease	5475 (9%)	1078 (8%)	2.0 (1.5, 2.6)
Cancer	3205 (5%)	1919 (14%)	2.0 (1.5, 2.6)
Schizophrenia	5562 (9%)	2516 (19%)	0.6 (0.4, 0.8)
Heart disease			
Conductive heart disease	3825 (6%)	645 (5%)	2.0 (1.5, 2.6)
Heart failure	5574 (9%)	801 (6%)	2.2 (1.7, 2.7)
Ischaemic heart disease	6630 (10%)	1138 (8%)	1.6 (1.2, 2.0)
Other heart disease	600 (1%)	115 (1%)	2.9 (1.7, 4.9)
Liver disease	844 (1%)	308 (2%)	2.6 (1.4, 4.9)
Senile dementia	4714 (7%)	715 (5%)	0.8 (0.6, 1.1)
<i>Drugs—ever in past</i>			
Adrenergic bronchodilator	8786 (14%)	1786 (13%)	1.8 (1.4, 2.2)
Angiotensin converting enzyme inhibitor	2702 (4%)	602 (4%)	2.0 (1.5, 2.7)
Antianginal	5193 (8%)	932 (7%)	1.7 (1.3, 2.1)
Antiarrhythmic	1099 (2%)	278 (2%)	2.0 (1.2, 3.2)
Antidiabetic	2201 (3%)	425 (3%)	1.7 (1.2, 2.4)
β-Blocker	9740 (15%)	1828 (13%)	1.1 (0.9, 1.5)
Calcium channel blocker	4909 (8%)	953 (7%)	1.5 (1.1, 1.9)
Cardiac glycoside	3745 (6%)	605 (4%)	2.4 (1.9, 3.1)
Coagulation modifier	904 (1%)	273 (2%)	2.2 (1.4, 3.5)
Lipid-lowering drug	427 (1%)	116 (1%)	1.1 (0.4, 3.6)
Systemic corticosteroid	5376 (8%)	1545 (11%)	1.8 (1.4, 2.3)
Thiazide	5315 (8%)	1027 (8%)	1.3 (1.0, 1.7)
Xanthine	2217 (3%)	476 (4%)	2.1 (1.5, 2.9)
<i>Drugs—current</i>			
Antiarrhythmic	239 (0.38%)	61 (0.45%)	3.3 (1.5, 6.9)
Antidepressant	18976 (30%)	2506 (18%)	1.1 (0.9, 1.4)
Cisapride	145 (0.23%)	46 (0.34%)	Inestimable
Erythromycin	660 (1%)	148 (1%)	3.0 (1.6, 5.4)
Loop diuretic	3373 (5%)	624 (5%)	2.0 (1.5, 2.5)
Potassium sparing diuretic	613 (1%)	144 (1%)	2.1 (1.3, 3.5)
Terfenadine/astemizole	270 (0.42%)	65 (0.48%)	1.1 (0.3, 4.4)

*Adjusted for sex, age, and receipt of thioridazine or haloperidol.

of a specific cause in elderly patients [16], who were common in this study (Table 1). The second possibility is that diagnoses of unexplained and unattended death in the GPRD have poor specificity for arrhythmic death. Therefore, we also examined as secondary outcome a narrower definition that excluded diagnoses of unexplained and unattended death.

Analysis

We used proportional hazards regression [17] to calculate the rate ratio for thioridazine *vs.* haloperidol. We adjusted for sex and age, as categorized in Table 1. We then individually examined the other variables listed in Table 1 (smoking status, diagnoses, and drugs) as potential confounders. If adding a variable changed the RR of interest by 10% or more, then that variable was considered a confounder and included in the final model [18].

Average daily dose was calculated for each patient, for each drug, by taking the total quantity of drug dispensed, divided by the duration of observation. We examined the effect of dose for each drug on the primary outcome, looking at the RR for each dose quartile *vs.* the lowest quartile. The effect of potential confounders on the RR for each dose quartile was examined as described above.

This study was approved by the University of Pennsylvania's Committee on Studies Involving Human Beings and the GPRD Scientific and Ethical Advisory Group.

Results

Table 1 presents the baseline characteristics of subjects by study group. Exposure to thioridazine was nearly five times as common as exposure to haloperidol. The age distributions were fairly advanced, particularly for the thioridazine group, where 45% of subjects were older than 75 years, *vs.* 31% in the haloperidol group. Most baseline variables had similar prevalences, although antidepressant use was more common in the thioridazine group, and cancer and schizophrenia were more common in the haloperidol group. Rate ratios between potential confounders and the outcome of interest are also presented in Table 1. Many factors that might be expected to be associated with sudden death and ventricular arrhythmia among antipsychotic drug users (e.g. cardiac conditions, loop diuretics) were in fact associated.

Table 2 presents the number of person-years of observation, events, rates, and rate ratios for the primary outcome, and for the secondary outcome that excluded unexplained/unattended death. The overall

Table 2

Comparison of the rate of diagnostic codes consistent with ventricular arrhythmia, cardiac arrest, sudden death, and unattended death between users of thioridazine and haloperidol

		Composite outcome of ventricular arrhythmia, sudden death, unexplained death, and unattended death			Narrower outcome defined by ventricular arrhythmia or sudden death		
		Rate per 1000 person-years	Unadjusted rate ratio (95% confidence interval) <i>vs.</i> haloperidol	Adjusted* rate ratio (95% confidence interval) <i>vs.</i> haloperidol	Rate per 1000 person-years	Unadjusted rate ratio (95% confidence interval) <i>vs.</i> haloperidol	Adjusted* rate ratio (95% confidence interval) <i>vs.</i> haloperidol
Subjects	Person-years of observation	Events			Events		
Thioridazine	63640	42018	381	9.1	1.1 (0.9, 1.4)	0.9 (0.7, 1.1)	1.4 (0.8, 2.6)
Haloperidol	13549	8336	69	8.3	1.0 (ref)	1.0 (ref)	1.0 (ref)
Total	77189	50354	450	8.9			

*Adjusted for sex and age. None of the variables listed in the appendix changed the rate ratio by 10% or more.

Table 3

Rate ratios for the composite outcome ventricular arrhythmia, sudden death, unexplained death, and unattended death for dose quartiles within study drugs, adjusted for age and sex

	Thioridazine Average daily dose in mg (thioridazine equivalents)	Number of subjects*	Number of events	Rate ratio (95% CI)†	Haloperidol Average daily dose in mg (thioridazine equivalents)	Number of subjects*	Number of events	Rate ratio (95% CI)†
Quartile 1	<18.8 (<18.8)	16029	67	1.0 (ref)	<1.0 (<40)	4555	17	1.0 (ref)
Quartile 2	18.8–31.2 (18.8–31.2)	16023	93	0.8 (0.6, 1.1)	1.0–1.7 (40–68)	2494	21	1.3 (0.7, 2.4)
Quartile 3	31.3–56.5 (31.3–56.5)	15888	116	0.9 (0.7, 1.2)	1.8–5.4 (72–216)	3130	24	1.5 (0.8, 2.8)
Quartile 4	>56.5 (>56.5)	15700	105	0.8 (0.6, 1.7)	>5.4 (>216)	3370	7	0.4 (0.2, 1.1)

*Ties did not permit division into exact quartiles.

†Adjusted for sex and age; other variables listed in Table 1 were not confounders.

event rate was 8.9 per thousand person-years for the primary composite outcome and 2.2 per thousand person-years when excluding unexplained and unattended death. The sex- and age-adjusted RR for thioridazine *vs.* haloperidol for the composite outcome was 0.9 (95% CI 0.7, 1.1; Table 1), and was not materially affected by other measured variables. The secondary analysis assuming a 15-day prescription duration showed a RR for thioridazine of 0.9 (95% CI 0.7, 1.3), while the secondary analysis assuming a 45-day prescription duration showed a RR for thioridazine of 0.8 (95% CI 0.6, 1.0). In the analysis that assumed a 30-day prescription duration and excluded unexplained and unattended death, the sex- and age-adjusted RR for thioridazine was 1.4 (95% CI 0.8, 2.6), and there were no other important confounders.

Table 3 presents the dose–response analysis for the primary outcome for each drug. Both drugs were used at low dose, with the dose of thioridazine being even lower than that of haloperidol when expressed in thioridazine equivalents. The rate did not appear to increase with dose for either drug over the range observed for the primary outcome (Table 3). There were not enough cases of the secondary outcome to perform dose–response analyses.

Discussion

Use of thioridazine and haloperidol

We found that relatively few users of thioridazine and haloperidol had a schizophrenia diagnosis. This is con-

sistent with earlier data from a subset of GPRD practices [19], and with the observed dose distribution, which indicated that most patients were being treated with doses lower than those typically used for schizophrenia. Our finding that thioridazine is used at a lower equivalent dose than haloperidol also agrees with results from other settings [9, 20].

Event rate

The rate of the primary outcome of ventricular arrhythmia, sudden death, and unexplained/unattended death was 8.9 per thousand person-years, which, given the advanced age of antipsychotic drug users observed, is roughly consistent with the rate of 4.1 per thousand person-years in the US population aged ≥ 35 years [21]. The rate of the narrower outcome of ventricular arrhythmia and sudden death of 2.1 per thousand person-years is roughly consistent with a prior study in the GPRD that found a crude rate of ventricular arrhythmia (an even narrower outcome) of 0.5 per thousand person-years in a population of current and past users of nonse- dating antihistamines [12].

Comparative cardiac safety of thioridazine and haloperidol

We found very similar rates of the primary outcome in users of thioridazine and haloperidol (adjusted RR 0.9, 95% CI 0.7, 1.1). In our secondary analysis, which excluded diagnoses of unexplained death and unattended death (i.e. excluded 76% of all outcomes), the adjusted RR for thioridazine was 1.4 (95% CI 0.8, 2.6). Neither result conflicts with our previous findings of no

difference at low dose [9]. Ray *et al.* did not report results comparing low-dose thioridazine and low-dose haloperidol [8]. Riley *et al.* studied psychiatric inpatients receiving a median daily thioridazine dose of 75 mg, and found that the odds ratio for sudden unexplained death associated with thioridazine was nine times as large as that for haloperidol, although the confidence intervals for the two drugs overlapped. While it is difficult to explain the apparent inconsistency between our results and those of Riley *et al.*, potential explanations include different study settings and outcomes, and the possibility that the apparent numeric difference found by Riley *et al.* could have been due to chance.

In the current study, the outcome rate did not increase with dose for either drug over the dosage range observed. This is in contrast to our earlier study, in which a positive dose–response relationship was evident for thioridazine, but not for haloperidol [9]. However, given that both drugs were used at much lower doses in the current study, we could easily have missed true relationships at higher doses. Therefore, our findings do not argue against dose–response relationships at doses above those seen in the current study. Although the effect of thioridazine on the QT interval depends in part on dose [22, 23], the relationship between particular degrees of QT prolongation and the risk of arrhythmias is poorly characterized [3].

Limitations

One limitation of this study is that the GPRD records medications as prescribed by the physician, rather than as dispensed by the pharmacy or as ingested by the patient. Therefore, recorded exposure may overestimate true exposure, and therefore dilute any true pharmacological effect of the drug. However, it seems unlikely that patients would continue to obtain prescriptions for a chronically used drug that they were not taking, and patients in the current study were followed for an average of 6 months. Another important limitation of this study is that we were only able to examine thioridazine and haloperidol at relatively low doses. Therefore, although these results are consistent with comparable cardiac safety at low doses, they do not argue against a difference at higher doses. An additional limitation is the possibility that differences in the usage patterns of the two drugs may have masked a true association. We attempted to limit this possibility by examining many potential confounders. An additional potential limitation is that cases of sudden death and ventricular arrhythmia may not be reliably documented in GPRD. However, previous studies have

shown that diagnoses in GPRD are reasonably complete [11], associations between drugs and ventricular arrhythmias have been demonstrated previously in the GPRD [12, 13], and a number of potential confounders were associated with the study outcome. Finally, and importantly, although our results suggest that low-dose thioridazine and haloperidol have similar cardiac safety, they do not argue against the possibility of effects shared by both drugs. However, because thioridazine appears to have a more pronounced effect on the QT interval than haloperidol (albeit at doses above those seen in this study [4]), and because prescribing information for thioridazine contains warnings for ventricular arrhythmia that are not shared by haloperidol, we believe that the current comparison provides clinically useful information.

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3282.00
3283.00
328z.00
4272d
4279e
4279ea
4279ec
4279gl
4279hv
7l1h.13
G571.00
G571.11
G574.00
G574000
G574011
G574100
G574z00
G575.00
G575.12
G575000
G575z00
G57ya00
K3093
Sp11000 | ECG: ventricular tachycardia
ECG: ventricular fibrillation
ECG: ventricular arrhythmia not otherwise specified
Cardiac arrest
Ventricular fibrillation
Arrhythmia ventricular (benign)
Ventricular ectopic beats
Ventricular flutter
Ventricular tachycardia paroxysmal
Defibrillation
Paroxysmal ventricular tachycardia
Ventricular tachycardia
Ventricular fibrillation and flutter
Ventricular fibrillation
Cardiac arrest–ventricular fibrillation
Ventricular flutter
Ventricular fibrillation and flutter not otherwise specified
Cardiac arrest
Asystole
Cardiac arrest with successful resuscitation
Cardiac arrest, unspecified
Re-entry ventricular arrhythmia
Defibrillation by catheter (i.v.)
Cardiac arrest as a complication of care |
|--|---|
-
<i>Sudden death</i>	
22j4.00
795 dr
795 n
G575100
R21.00
R211.00
R21z.00
Ryuc100
T4002	On exam – dead–sudden death
Dropped dead
Death sudden nonviolent
Sudden cardiac death, so described
Sudden death, cause unknown
Instantaneous death
Sudden death, cause unknown not otherwise specified
Other sudden death, cause unknown
Sudden death
-
<i>Unexplained and unattended death</i>	
22j1.00
22j3.00
7962
7963
R212.00
R212z00
R213.00
R213000
R213100
R213z00	On exam – dead–unexpected
On exam – dead–unattended death
Dead when found
Cause of death unknown
Death less than 24 h from onset
Death less than 24 h from onset
Unattended death
Found after death, unknown cause of
Found dead
Unattended death not otherwise specified

Appendix

Diagnosis codes used

Ventricular arrhythmia

2241.00	On exam—collapse, cardiac arrest
328.00	ECG: ventricular arrhythmia