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Domperidone and Ventricular Arrhythmia or Sudden Cardiac Death

A Population-Based Case-Control Study in the Netherlands

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Abstract

Background: Recently, a 4-fold increase in risk of sudden cardiac death (SCD) was reported for domperidone in a study that focused on corrected QT interval (QTc)-prolonging drugs as a class and their association with SCD.

Objective: To evaluate the association between the use of domperidone and serious non-fatal ventricular arrhythmia (VA) and SCD in the general population.

Methods: We performed a population-based, case-control study during 1996–2007 in the Integrated Primary Care Information (IPCI) database, a longitudinal general practice research database in the Netherlands. We included all patients aged ≥18 years without cancer in the source population. We studied the association between the use of domperidone by recency of use (current, past and none) and daily dose, and the risk of serious non-fatal VA or SCD. Cases were defined as a natural death due to cardiac causes heralded by abrupt loss of consciousness within 1 hour after the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition <24 hours previously with no evidence of a non-cardiac cause. Controls were randomly drawn from the source population and matched to cases on age, sex, practice and index date. We compared the exposure odds for SCD alone and VA plus SCD by means of conditional logistic regression while adjusting for all available confounders. In addition, we stratified by insurance type.

Results: The study population comprised 1366 cases (62 VA and 1304 SCD) and 14 114 matched controls. Of all cases, ten patients were current domperidone users at the index date, all with SCD. The matched unadjusted odds ratio of domperidone and SCD was 3.72 (95% CI 1.72, 8.08). Daily doses >30 mg were associated with a significant increased risk of SCD (adjusted odds ratio [OR_{adj}] 11.4 [95% CI 1.99, 65.2]). Since there was a near interaction with health insurance ($p = 0.050$), all analyses were stratified by insurance. In publicly insured patients, seven cases were current users at the index date.

Current use was associated with a significant increased risk of SCD (OR_{adj} 4.17 [95% CI 1.33, 13.1]). Amongst privately insured patients there was one domperidone-exposed case, and amongst non-insured there were two.

Conclusions: Current use of domperidone, especially high doses, is associated with an increased risk of SCD. We could not demonstrate an effect of domperidone on non-fatal VA due to absence of exposed cases.

Background

Domperidone is a peripheral dopamine D_2-receptor antagonist with gastrokinetic and antiemetic properties, and has been marketed since March 1978 as a prescription drug for the following indications: nausea, vomiting and dyspepsia associated with motility disorders.[1] In many countries, such as the Netherlands, domperidone is also available as an over-the-counter (OTC) product for the treatment of nausea and dyspepsia associated with motility disorders. In the Netherlands, domperidone was available as an OTC drug, but reimbursement was possible when prescribed. As of January 2004, domperidone was no longer reimbursed, even when prescribed. As of January 2005, the drug was reimbursed in long-term use (>6 months).

A recent epidemiological study[2] conducted in the Netherlands evaluated the use of non-cardiac heart rate-corrected QT (QTc) interval-prolonging drugs and the risk of sudden cardiac death (SCD). In a sub-analysis it was found that domperidone increased the risk of SCD almost 4-fold.[2] Since the study was not primarily focused on individual drugs, and modelling was not specific for the individual drugs, the marketing authorization holder asked for a more specific study that would focus on domperidone and would include not only SCD but also non-fatal ventricular arrhythmias (VAs).

Prolongation of the QTc interval, which is the traditional measurement for assessing the duration of ventricular repolarization, life-threatening ventricular tachyarrhythmias and even cardiac arrests, has been reported after intravenous use of domperidone; however, causality assessment has often been confounded by concomitant medications and co-morbidity.[3] Prolongation of ventricular repolarization may result in early after depolarizations (EADs), which in turn may induce re-entry and thereby provoke Torsade de Pointes (TdP) and fatal VAs.[4-8]

Inhibition of the human ether-à-go-go-related gene (*hERG*), which encodes a delayed rectifier K^+ current, leads to prolongation of the QTc interval.[9] Domperidone has been shown to inhibit the *hERG* current and to cause a significant prolongation of cardiac repolarization.[3] Domperidone is mainly metabolized via the cytochrome P450 (CYP) 3A4 isoenzyme; *in vitro* data indicate that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma concentrations of domperidone. Even though no effect on QTc was seen with oral domperidone as monotherapy, prolongation of the QTc interval was observed when combined with ketoconazole, a CYP3A4 inhibitor.[10]

The primary purpose of this study was to evaluate the association between use of domperidone and serious fatal (SCD) and non-fatal VA, while controlling specifically for confounding factors in this association. This was done in the same database as that used for the initial study,[2] but also included VA and was updated until 2007.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) database, a longitudinal database of electronic medical records from general practitioners (GPs) in the Netherlands. In the Dutch healthcare system, the GP has a pivotal role by acting as a gatekeeper for all medical care. Nearly every citizen is enrolled in the practice of a GP independent of

health status.[11] Details of the database have been described elsewhere.[11,12] Briefly, the database currently contains the complete medical records of 1 million citizens. The electronic records contain coded (using the International Classification for Primary Care[13] and free text) and narrative data on demographics, healthcare insurance (public or private as a proxy for income), symptoms and diagnoses from GPs and specialists, referrals, laboratory findings, hospitalizations and drug prescriptions, including their indications and dosage regimen. To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The project complies with EU guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research in several validation studies that evaluated the quality of the available information.[12] The Scientific and Ethics Advisory Board of the IPCI project approved this study (project number 07/07).

Source Population

The source population comprised all patients aged 18 years and older in the IPCI database with a valid database history of at least 1 year. Follow-up started whenever all entrance criteria (1 year of valid database capture, age 18 years, and 1 January 1995) were reached. All subjects in the source population were followed until the occurrence of the outcome of interest (SCD, non-fatal VA or the earliest of both), cancer (exclusion criterion), death, transferring out of the practice, date of last data collection from the GP or end of the study (1 May 2007), whichever came first. The study population comprised all cases with serious VA or SCD occurring in the source population during the study period and their matched controls.

Case and Control Definition

The primary outcome of interest was serious idiopathic VA (ventricular fibrillation [VF] or TdP) and SCD. Potential cases were identified through a sensitive search on codes and narratives. Subsequently, the medical records of all potential cases were reviewed manually to assess whether death could be classified as SCD or whether non-fatal VA could be classified as VF or TdP. Initial validation was performed independently by two medically trained persons who were blinded to exposure and classified cases as potential or non-cases. All potential cases were reassessed by a specialized physician and classified as probable or definite.

Case assessment of SCD was based on the most recent definition of SCD: a natural death due to cardiac causes heralded by abrupt loss of consciousness within 1 hour after the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition <24 hours previously with no evidence of a non-cardiac cause.[14] Cases were classified as SCD if the medical record indicated that death occurred within 1 hour after the onset of symptoms, and if the following wording was found in the free text: 'sudden cardiac death', 'acute cardiac death', 'mors subita', 'sudden death', 'died suddenly', 'died unexpectedly' or if this was an unwitnessed, unexpected death of someone seen in 'good health' or in a stable medical condition 24 hours previously and without evidence of a non-cardiac cause (e.g. pneumonia, convulsion, choking, stroke or suicides). The assessment of SCD was done independently of the previous assessment of SCD in the same database (Straus et al.[2]) and was more strict regarding any prior symptoms in the unwitnessed cases to avoid protopathic bias (specifically for domperidone) due to chest pain.

Non-fatal VA cases were identified by broad searching on the following codes or text words/abbreviations: 'collapse', 'VES', 'VF', 'ventricular & arrhythmia', 'PVC', 'ventricle', 'tachycardia', 'Torsade', 'VT', 'rhythm disturbance', 'flutter', 'cardioversion', 'defibrill*', 'QRS', 'QTc', 'ECG abnormalities', 'death' and ICPC diagnosis codes 'K79', 'K80, 'K84'. All potential cases either had been referred or seen by a cardiologist or an ECG was performed. All non-fatal VA cases were divided in TdP (diagnosis made by a specialist with the help of an ECG) or VF (diagnosis by an ECG). For all VAs it was assessed whether they occurred as primary or secondary disorder (i.e. as primary disorder or after myocardial infarction). The date

of onset of VA was assessed based on the information in the electronic medical record (including free text). All assessments were done while being blinded to exposure.

To each case, up to 20 (SCD) or 40 (non-fatal VA) controls were randomly drawn from the source population matched on age (year of birth), sex and practice. The index date was defined as the date on which VA or SCD occurred in the cases. This date was also the index date for matched controls.

Exposure Definition

The exposure of interest was use of domperidone. In order to classify use at the index date, we calculated the duration of each prescription, by dividing the total number of units issued per prescription by the number of units prescribed daily. Exposure at the index date was categorized into three mutually exclusive groups of current, past, and never use. Since domperidone is normally prescribed for shorter periods of time, use was defined as current if the index date fell within a period of use or within a maximum of 7 days after the end of the last prescription to account for carry-over effects. Past use was defined as more than 7 days prior to the index date. If patients had no prescription prior to the index date they were considered non-exposed. If domperidone was prescribed 'as needed', the GP estimated duration was taken if available, otherwise a default of 30 days was taken. If a refill was prescribed, the duration of exposure was extended. Among current users, we evaluated the effect of daily dose (<30, 30 mg [1 defined daily dose] and >30 mg), which allows for dose-response assessment.

To better study the effect of stopping and potential confounding by indication, we subcategorized past exposure into recent past exposure (stopping between 8 days and 3 months), moderate past exposure (3–6 months), distant past exposure (6–12 months previous) and very distant past exposure (>1 year prior to index date).

Co-Variates

Known risk factors for VA/SCD and other co-variates were gathered from medical records. Cerebrovascular ischaemia, cardiovascular ischaemia, heart failure, depression, schizophrenia, epilepsy, neuropathy, dyspepsia and chronic obstructive pulmonary disease were assessed, based on the diagnoses provided by the GP and specialists in the medical records. Hypertension was identified through the diagnoses in the medical records, use of antihypertensive medication and/or blood pressure measurements, according to the guidelines of the WHO (a blood pressure exceeding 140 mmHg systolic and/or 90 mmHg diastolic).[15] Diabetes mellitus and hypercholesterolaemia were identified through a diagnosis in the medical records from GPs and specialists and/or use of antidiabetic or lipid-lowering medication. Diabetic gastropathy (nausea, vomiting, heartburn, abdominal bloating and early fullness in persons with diabetes) was assessed through manual review of the patient's files in the year prior to the index date. Information on smoking and alcohol abuse was obtained from the codes and narratives in the medical records. As concomitant medication, we considered QTc-prolonging drugs as specified in the most recent version of list 1 (drugs that are generally accepted by authorities to have a risk of causing TdP).[16] Furthermore, we considered drugs that may interact with domperidone metabolism (CYP3A4-inhibiting and -inducing drugs), drugs that affect *hERG*, digoxin, diuretics, laxatives, systemic β-adrenergic receptor agonists and oral corticosteroids. Co-variate drug use was classified as current (prescription duration covers the index date or stopped <8 days ago), past (stopped at index date between 8–365 days) or never use. As a proxy for health status, the number of GP office visits in the year prior to the index date was assessed by the total number of office/home visits during the 1 year prior.

Statistical Analysis

Prescription rates (number of users per year) of domperidone were calculated in the source population and stratified by healthcare insurance to inspect potential differential misclassification due to insurance (since the drug is mostly OTC and reimbursed). The association between VA/SCD and the co-variates was assessed through

conditional logistic regression analysis separately for SCD as well as together with VA. Interaction of the association between domperidone exposure and specific co-variates (age, sex, insurance type) was tested on the basis of multiplicative interaction using logistic regression (with the matching factors as co-variates). In addition, we stratified for type of healthcare insurance.

All co-variates that were univariately associated with the outcome ($p < 0.10$) were considered as potential confounders. Subsequently, the multivariate models were built to include all co-variates that changed the association between current use of domperidone and the outcome by more than 5% (i.e. 0.95 > adjusted odds ratio [OR_{adj}]/unadjusted odds ratio [OR_{unadj}] > 1.05). Although GP visits have no aetiological relationship with the outcome, we additionally adjusted for the number of GP visits in the previous year as a proxy for health status.

Sensitivity analyses were conducted to investigate various sources of bias and residual confounding. First, the effect of residual confounding by diabetic gastroparesis was addressed by excluding all diabetes patients. In addition, we conducted an analysis that excluded all patients with prior cardiovascular disease (heart failure and myocardial infarction) to avoid residual confounding due to severity of underlying cardiovascular disease. Additional misclassification of exposure due to unmeasured OTC use of domperidone was inspected by censoring at 1 January 2004, which was the date that prescribed domperidone was no longer reimbursed, thereby taking away any incentive to get the drug on prescription.

Results

The source population for this study comprised 478 661 subjects with at least 1 year of valid history during the study period. Figure 1 shows the prevalence of domperidone use in the source population over calendar time by type of healthcare insurance. Publicly insured persons had a higher prevalence of recorded domperidone use than privately insured patients, but in 2004 (when reimbursement was lifted for all OTC drugs even when prescribed) the prevalence dropped in publicly insured patients and remained stable in privately insured patients, pointing to differential misclassification by insurance type.

Overall, 926 persons were classified as definite SCD and 498 as probable SCD (table I). After exclusion of 120 cases with cancer prior to the index date, the study population comprised 1304 cases of SCD and 13 480 matched controls. The mean age of the cases was 72.5 years and 58% were male.

Of the potential VA cases, 287 were classified as definite VF, and 6 as TdP; however, only 57 VF cases and 6 TdP cases were not preceded by other disease (such as myocardial infarction). Of these 63 persons, 21 died within 30 days after the onset of VA. After exclusion of one case with cancer prior to the index date, the study population

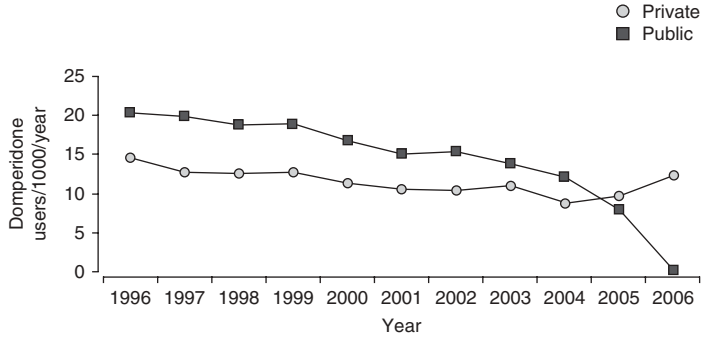

Fig. 1. Prevalence of domperidone use per thousand persons by calendar year.

Table I. Baseline characteristics, demographics, distribution of co-variates[a,b]

Characteristic	Sudden cardiac death			Serious ventricular arrhythmia		
	cases (n = 1304)	controls (n = 13 480)	OR (95% CI)	cases (n = 62)	controls (n = 634)	OR (95% CI)
Males	755 [57.9]	8211 [60.9]		41 [66.1]	439 [69.2]	
Age (mean ± SD) [y]	72.5 ± 14.1	66.3 ± 13.9		64.9 ± 15.2	61.6 ± 14.1	
≤55	166 [12.7]	2938 [21.8]		13 [21.0]	212 [33.4]	
55–65	180 [13.8]	2733 [20.3]		14 [22.6]	146 [23.0]	
66–75	330 [25.3]	3948 [29.3]		20 [32.3]	171 [27.0]	
>75	628 [48.2]	3861 [28.6]		15 [24.2]	105 [16.6]	
Co-morbidities						
Ischaemic cerebro-/cardiovascular disease	385 [29.5]	1916 [14.2]	*2.01 (1.74, 2.33)*	22 [35.5]	62 [9.8]	*5.43 (2.77, 10.66)*
Angina	294 [22.5]	1408 [10.4]	*2.04 (1.74, 2.39)*	19 [30.6]	46 [7.3]	*6.44 (3.13, 13.25)*
Myocardial infarction	64 [4.9]	234 [1.7]	*2.64 (1.92, 3.64)*	5 [8.1]	11 [1.7]	*5.14 (1.39, 19.03)*
Transient ischaemic attack	59 [4.5]	339 [2.5]	1.22 (0.90, 1.66)	2 [3.2]	11 [1.7]	1.54 (0.31, 7.77)
Cerebrovascular accident	51 [3.9]	215 [1.6]	1.76 (1.25, 2.48)	1 [1.6]	3 [0.5]	2.75 (0.28, 27.29)
Hypertension	487 [37.3]	4103 [30.4]	*1.24 (1.09, 1.42)*	20 [32.3]	167 [26.3]	1.01 (0.51, 1.99)
Diabetes mellitus	258 [19.8]	1165 [8.6]	*2.47 (2.10, 2.91)*	10 [16.1]	51 [8.0]	1.77 (0.73, 4.27)
Diabetic gastropathy	30 [2.3]	138 [1.0]	*2.06 (1.34, 3.17)*	1 [1.6]	4 [0.6]	2.76 (0.31, 24.85)
Heart failure	237 [18.2]	536 [4.0]	*4.00 (3.29, 4.85)*	9 [14.5]	9 [1.4]	*7.37 (2.35, 23.06)*
Hypercholesterolaemia	178 [13.7]	1459 [10.8]	*1.56 (1.30, 1.88)*	16 [25.8]	82 [12.9]	*4.41 (2.08, 9.35)*
Depression	91 [7.0]	699 [5.2]	*1.40 (1.10, 1.79)*	5 [8.1]	33 [5.2]	1.40 (0.42, 4.62)
Schizophrenia	11 (0.8)	20 (0.1)	*6.14 (2.74, 13.8)*	0 (0)	0 (0)	NA
Chronic obstructive lung disease	183 [14.0]	1118 [8.3]	*1.58 (1.31, 1.90)*	11 [17.7]	63 [9.9]	1.80 (0.77, 4.24)
Epilepsy	15 [1.2]	63 [0.5]	*2.39 (1.29, 4.43)*	0 (0)	1 [0.2]	NA
Neuropathy	23 [1.8]	260 [1.9]	0.84 (0.53, 1.32)	2 [3.2]	14 [2.2]	1.45 (0.30, 7.10)
Dyspepsia	319 [24.5]	2741 [20.3]	*1.18 (1.02, 1.38)*	13 [21.0]	126 [19.9]	1.13 (0.56, 2.27)
Lifestyle						
Smoking	256 [19.6]	2631 [19.5]	*1.33 (1.13, 1.56)*	16 [25.8]	134 [21.1]	1.64 (0.81, 3.31)
Alcohol abuse	24 [1.8]	97 [0.7]	*3.31 (2.04, 5.36)*	0 [0]	7 [1.1]	NA
Public insurance	831 [63.7]	5932 [44.0]	*2.66 (2.30, 3.08)*	28 [45.2]	366 [57.7]	1.97 (0.96, 4.05)
Number of GP visits [mean ± SD]	6.7 ± 7.8	4.3 ± 5.0	*1.05 (1.04, 1.07)*	5.4 ± 5.2	3.6 ± 4.1	*1.08 (1.01, 1.16)*
Concomitant medication						
QTc-prolonging drugs	53 [4.1]	260 [1.9]	*2.11 (1.52, 2.92)*	7 [11.3]	13 [2.1]	*8.30 (2.43, 28.31)*

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Table I. Contd

Characteristic	Sudden cardiac death			Serious ventricular arrhythmia		
	cases (n = 1304)	controls (n = 13 480)	OR (95% CI)	cases (n = 62)	controls (n = 634)	OR (95% CI)
hERG-inhibiting drugs	139 [10.7]	813 [6.0]	*1.82 (1.48, 2.24)*	10 [16.1]	43 [6.8]	*2.92 (1.19, 7.18)*
CYP3A4-inducing drugs	10 [0.8]	40 [0.3]	*2.33 (1.08, 5.05)*	0 [0]	0 [0]	NA
CYP3A4-inhibiting drugs	59 [4.5]	277 [2.1]	*1.83 (1.34, 2.50)*	1 [1.6]	13 [2.1]	NA
Drugs for dyspepsia and GORD (H_2RAs and PPIs)	97 [7.4]	840 [6.2]	1.08 (0.85, 1.37)	2 [3.2]	40 [6.3]	0.28 (0.04, 2.09)
Laxatives	81 [6.2]	378 [2.8]	*1.77 (1.33, 2.34)*	1 [1.6]	16 [2.5]	NA
Digoxin	112 [8.6]	287 [2.1]	*3.74 (2.91, 4.82)*	5 [8.1]	13 [2.1]	3.19 (0.89, 11.44)
Diuretics	220 [16.9]	810 [6.0]	*3.23 (2.67, 3.89)*	8 [12.9]	33 [5.2]	*2.86 (1.12, 7.26)*
Corticosteroids	36 [2.8]	115 [0.1]	*2.49 (1.65, 3.75)*	0 (0)	0 [0]	NA
β-Adrenergic receptor agonists	134 [10.3]	775 [5.7]	*1.94 (1.26, 2.21)*	0 (0)	0 [0]	NA

a All values are presented as n [%] unless otherwise stated.

b Italicized text denotes statistically significant associations.

CYP = cytochrome P450; **GORD** = gastro-oesophageal reflux disease; **GP** = general practitioner; **H_2RAs** = histamine H_2 receptor antagonists; ***hERG*** = human ether-à-go-go-related gene; **NA** = not applicable (<3 cases); **OR** = odds ratio (matched for age, sex, index date and practice); **PPIs** = proton pump inhibitors.

comprised 62 cases of VA and 634 matched controls. There were no currently exposed cases to domperidone, which hampers the possibility to assess the association between VA and prescribed domperidone.

Domperidone and Sudden Cardiac Death

Of all SCD cases, ten patients were current domperidone users at the index date and 94 patients were past users (table II). The OR_{unadj} of domperidone and SCD was 3.72 (95% CI 1.72, 8.08). There was a suggestion of an interaction with health insurance ($p = 0.050$) but not with age ($p = 0.547$) and sex ($p = 0.491$). Because of the suggestion of an interaction with insurance type, all subsequent analyses were stratified by type of healthcare insurance.

Seven of the currently exposed domperidone cases were publicly insured, one patient privately and two patients had no registered insurance. Current use of domperidone was associated with SCD in the entire population, although this was no longer significant when adjusting also for GP visits (table II). This strong effect of GP visits was mostly due to the strong correlation between GP visits and type of healthcare insurance ($p < 0.0001$). Publicly insured patients visited the GP with a mean of 5.0 visits in the last year (SD 5.9), whereas privately insured patients visited the GP with a mean of 4.0 visits in the last year (SD 4.6).

In publicly insured persons, current use of domperidone was associated with a significantly increased risk of SCD after adjustment for heart failure, *hERG*-inhibiting drugs, laxatives, diuretics, corticosteroids and digoxin (OR 4.98; 95% CI 1.59, 15.6). The association between current use of domperidone and SCD decreased slightly after further adjustment for GP visit frequency (OR 4.17; 95% CI 1.33, 13.1). Past use of domperidone was not associated with SCD after adjustment for GP visit frequency. In privately and non-insured patients we could not estimate the adjusted effect of current use of domperidone because of small numbers of exposed persons. The matched OR_{unadj} for current use was 0.78 (95% CI 0.09, 6.81) for privately insured patients and 1.73 (95% CI 0.10, 30.8) for non-insured patients (data not shown).

Table II. Risk of sudden cardiac death[a]

Use of domperidone	Cases	Controls	OR (95% CI)[b]	OR (95% CI)[c]	OR (95% CI)[d]
Overall population	1304	13480			
Never use	1200	12781	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	94	671	*1.56 (1.23, 1.98)*	*1.36 (1.05, 1.75)*	1.28 (0.99, 1.65)
recent past (8 d–3 mo)	10	54	1.91 (0.95, 3.86)	1.56 (0.73, 3.33)	1.39 (0.65, 2.99)
moderate past (3–6 mo)	7	34	2.30 (0.98, 5.38)	2.24 (0.93, 5.41)	2.00 (0.83, 4.86)
distant past (6–12 mo)	13	83	1.59 (0.86, 2.96)	1.26 (0.67, 2.39)	1.03 (0.53, 2.00)
very distant past (>12 mo)	64	500	*1.46 (1.09, 1.94)*	1.29 (0.95, 1.75)	1.26 (0.93, 1.70)
Current use	10	28	*3.72 (1.72, 8.08)*	*2.44 (1.01, 5.89)*	1.99 (0.80, 4.96)
<30 mg	2	10	NA	NA	NA
30 mg	4	15	2.57 (0.79, 8.36)	1.41 (0.38, 5.32)	1.02 (0.23, 4.42)
>30 mg	4	3	*16.0 (3.49, 73.6)*	*11.2 (2.02, 62.45)*	*11.4 (1.99, 65.2)*
Stratified by insurance					
Publicly insured	831	5932			
Never use	759	5615	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	65	305	*1.77 (1.28, 2.44)*	*1.47 (1.05, 2.08)*	1.34 (0.94, 1.90)
Current use	7	12	*4.46 (1.46, 13.7)*	*4.98 (1.59, 15.6)*	*4.17 (1.33, 13.1)*
<30 mg	1	5	NA	NA	NA
30 mg	3	7	3.02 (0.67, 13.7)	3.27 (0.70, 15.3)	2.57 (0.54, 12.2)
>30 mg	3	0	NA	NA	NA
Privately insured	412	7289			
Never use	387	6918	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	24	358	1.47 (0.87, 2.48)	1.26 (0.72, 2.20)	1.22 (0.70, 2.12)
Current use	1	13	NA	NA	NA
Not insured	61	259			
Never use	54	248	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	5	8	2.05 (0.40, 10.4)	1.53 (0.25, 9.40)	1.11 (0.15, 8.47)
Current use	2	3	NA	NA	NA

a Italicized text denotes statistically significant associations.

b OR matched for age, sex, practice and index date.

c Overall population: OR adjusted for heart failure, insurance type, CYP3A4 inhibitors, *hERG*-inhibiting drugs, laxatives, digoxin, diuretics, corticosteroids, β-adrenergic receptor agonists. Publicly insured: OR adjusted for heart failure, *hERG*-inhibiting drugs, laxatives, diuretics, corticosteroids and digoxin. Privately insured: OR adjusted for heart failure, diuretics, corticosteroids, β-adrenergic receptor agonists and digoxin. Not insured: OR adjusted for heart failure, diuretics, corticosteroids, CYP3A4 inhibitors, *hERG*-inhibiting drugs, digoxin and β-adrenergic receptor agonists.

d Additionally adjusted for general practitioner visits.

CYP = cytochrome P450; ***hERG*** = human ether-à-go-go-related gene; **NA** = not applicable (<3 cases); **OR** = odds ratio; **ref** = reference.

A high daily prescribed dose (>30 mg for the total population) was associated with a higher risk of SCD after complete adjustment, i.e. including GP visits (11.4; 95% CI 1.99, 65.2) than normal (30 mg) or low dosages (<30 mg) [1.02 (95% CI 0.23, 4.42) and 1.24 (95% CI 0.19, 8.12), respectively]. After stratification for insurance, dose response could not be assessed in the separate categories because of small numbers. We aggregated high and normal dose for publicly insured patients (OR_{adj} 7.21 [95% CI 2.03, 25.6]).

Domperidone and Ventricular Arrhythmia/Sudden Cardiac Death

In order to assess the association between VA/SCD and domperidone, we combined the SCD and VA datasets, censoring 17 SCD cases at

the time at which VA occurred, as they were also included in the VA set (as they had confirmed VA). High-dose domperidone (>30 mg) was associated with a significantly increased risk of SCD/VA (11.4 [95% CI 1.99, 64.9]) in the total population after complete adjustment (table III); however, this was in fact the SCD effect.

Sensitivity Analyses

In view of the possibility of residual confounding by diabetic gastroparesis we excluded diabetes patients (table IV). This increased the association between current use of domperidone and SCD to 5.12 (95% CI 2.01, 13.0) and also the dose-response relationship to 54.2 (95% CI 4.95, 592.6).

Exclusion of cardiovascular diseases increased the association between current use of domperidone and SCD after complete adjustment (4.05 [95% CI 1.60, 10.2]) and increased the dose response relationship (high daily prescribed dose [>30 mg]) [35.8 (95% CI 3.68, 347.5)].

Exclusion of all case- and matched-control sets (matched on index date) with index dates after 1 January 2004 (when domperidone was no longer reimbursed if prescribed) did not materially change the association of current use of domperidone and SCD (2.03 [95% CI 0.77, 5.36]) and the dose

Table III. Risk of sudden cardiac death and non-fatal ventricular arrhythmia[a]

Use of domperidone	Cases	Controls	OR (95% CI)[b]	OR (95% CI)[c]	OR (95% CI)[d]
Overall population	1 366	14 114			
Never use	1 258	13 384	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	98	700	*1.57 (1.24, 1.99)*	*1.35 (1.05, 1.73)*	1.26 (0.98, 1.62)
Current use	10	30	*3.54 (1.64, 7.64)*	2.35 (0.99, 5.62)	1.92 (0.78, 4.73)
<30 mg	2	11	NA	NA	NA
30 mg	4	16	2.45 (0.76, 7.86)	1.36 (0.37, 5.04)	0.99 (0.23, 4.23)
>30 mg	4	3	*16.0 (3.48, 73.4)*	*11.2 (2.02, 62.3)*	*11.4 (1.99, 64.9)*
Publicly insured	865	6 194			
Never use	790	5 858	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	68	323	*1.76 (1.28, 2.41)*	*1.46 (1.04, 2.04)*	1.32 (0.94, 1.86)
Current use	7	13	*4.45 (1.45, 13.6)*	*4.13 (1.32, 13.0)*	*4.92 (1.58, 15.4)*
<30 mg	1	5	NA	NA	NA
30 mg	3	8	3.03 (0.67, 13.7)	3.24 (0.69, 15.1)	2.56 (0.54, 12.1)
>30 mg	3	0	NA	NA	NA
Privately insured	440	7 655			
Never use	414	7 274	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	25	367	1.45 (0.87, 2.42)	1.24 (0.72, 2.14)	1.20 (0.70, 2.05)
Current use	1	14	NA	NA	NA
Not insured	61	265			
Never use	54	252	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	5	10	2.05 (0.10, 30.8)	1.53 (0.25, 9.40)	1.11 (0.15, 8.47)
Current use	2	3	NA	NA	NA

a Italicized text denotes statistically significant associations.

b OR matched for age, sex, practice and index date.

c Overall population: OR adjusted for heart failure, insurance type, CYP3A4 inhibitors, *hERG*-inhibiting drugs, laxatives, digoxin, diuretics, corticosteroids, β-adrenergic receptor agonists. Publicly insured: OR adjusted for heart failure, *hERG*-inhibiting drugs, laxatives, diuretics, corticosteroids and digoxin. Privately insured: OR adjusted for heart failure, diuretics, corticosteroids, β-adrenergic receptor agonists and digoxin. Not insured: OR adjusted for heart failure, diuretics, steroids, CYP3A4 inhibitors, *hERG*- inhibiting drugs, digoxin and β-adrenergic receptor agonists.

d Additionally adjusted for general practitioner visits.

CYP = cytochrome P450; ***hERG*** = human ether-à-go-go-related gene; **NA** = not applicable (<3 cases); **OR** = odds ratio; **ref** = reference.

Table IV. Risk of sudden cardiac death, sensitivity analyses[a]

Use of domperidone	Exclusion of diabetes mellitus			Exclusion of cardiovascular diseases			Censoring at 1 January 2004		
	cases	controls	OR (95% CI)[b]	cases	controls	OR (95% CI)[b]	cases	controls	OR (95% CI)[b]
Total population	1 046	12 315		1 027	12 753		1 044	10 892	
Never use	969	11 701	1.0 (ref)	953	12 125	1.0 (ref)	956	10 351	1.0 (ref)
Past use	67	592	1.23 (0.90, 1.67)	65	605	1.26 (0.93, 1.71)	79	518	*1.40 (1.05, 1.85)*
Current use	10	22	*5.12 (2.01, 13.0)*	9	23	*4.05 (1.60, 10.2)*	9	23	2.03 (0.77, 5.36)
<30 mg	2	9	NA	1	9	NA	2	7	NA
30 mg	4	11	*4.07 (1.06, 15.7)*	4	12	2.45 (0.67, 8.96)	3	13	0.70 (0.12, 4.03)
>30 mg	4	2	*54.2 (4.95, 592.6)*	4	2	*35.8 (3.68, 347.5)*	4	3	*11.6 (2.08, 64.6)*
Publicly insured	661	5 354		652	5 574		676	4 995	
Never use	608	5 078	1.0 (ref)	602	5 287	1.0 (ref)	615	4 727	1.0 (ref)
Past use	46	265	1.25 (0.81, 1.93)	44	275	1.38 (0.91, 2.11)	54	257	1.37 (0.94, 2.01)
Current use	7	11	*6.07 (1.81, 20.4)*	6	12	*4.11 (1.25, 13.6)*	7	11	*4.17 (1.33, 13.0)*
<30 mg	1	5	NA	0	5	NA	1	4	NA
30 mg	3	6	4.79 (0.86, 26.9)	3	7	2.15 (0.43, 10.7)	3	7	2.55 (0.54, 12.1)
>30 mg	3	0	NA	3	0	NA	3	0	NA
Privately insured	338	6 727		325	6 951		325	6 951	
Never use	318	6 397	1.0 (ref)	306	6 618	1.0 (ref)	306	6 618	1.0 (ref)
Past use	19	320	1.38 (0.72, 2.66)	18	323	1.35 (0.72, 2.55)	18	323	1.35 (0.72, 2.55)
Current use	1	10	NA	1	10	NA	1	10	NA

a Italicized text denotes statistically significant associations.

b Overall population: OR matched for age, sex, practice and index date and adjusted for heart failure, insurance type, CYP3A4 inhibitors, *hERG*-inhibiting drugs, laxatives, digoxin, diuretics, corticosteroids, β-adrenergic receptor agonists and GP visits. Publicly insured: OR matched for age, sex, practice and index date, and adjusted for heart failure, *hERG*-inhibiting drugs, laxatives, diuretics, corticosteroids, digoxin and GP visits. Privately insured: OR matched for age, sex, practice and index date, and adjusted for heart failure, diuretics, corticosteroids, β-adrenergic receptor agonists, digoxin and GP visits.

CYP = cytochrome P450; **GP** = general practitioner; ***hERG*** = human ether-à-go-go-related gene; **NA** = not applicable (<3 cases); **OR** = odds ratio; **ref** = reference.

response relationship (high daily prescribed dose (>30 mg) [95% CI 11.6 (2.08, 64.6)].

Discussion

This study was conducted to specifically investigate the association between use of domperidone and the occurrence of serious VAs. We demonstrated that current use of domperidone, in particular high dose, was associated with a substantial increased risk of SCD. We could not assess the risk of VA since there were no exposed VA cases. Past use of domperidone was not significantly associated with an increased risk of SCD, although recent exposure was associated with a slightly elevated risk.

Inhibition of the *hERG*-encoded potassium channels leads to prolongation of the QTc interval, which can degenerate into VAs and eventually lead to SCD.[9] Domperidone has been shown to inhibit the *hERG*-encoded potassium channels and thereby cause a significant prolongation of cardiac repolarization.[3] The main metabolic pathway of domperidone is via the CYP3A4 isoenzyme. Concomitant use of drugs that inhibit this enzyme may result in increased plasma concentrations of domperidone. Studies in healthy volunteers have demonstrated prolongation of the QTc interval when domperidone was combined with ketoconazole, a CYP3A4 inhibitor. When oral domperidone was used as monotherapy, no effect on QTc was seen.[10]

The current study was a result of the study by Straus et al.[2] and is based on the same database, but it differs from the initial publication for various reasons. First, the model was specifically

built around domperidone alone and not around use of non-cardiac QTc-prolonging agents in general. Second, because of the potential of protopathic bias due to chest pain and stomach ache, cases of SCD were validated more strictly, excluding all those who might have vague chest symptoms. Third, the number of cases was larger since the study by Straus et al.[2] ended in 2003, although the cases exposed to domperidone in the previous study (n = 9) overlap with the current study (n = 10). Fourth, the analysis now also looked at dose response. Despite the fact that the modelling was specific for domperidone, conclusions were the same although more refined, namely that domperidone in high dosages is associated with SCD in the general population. In the future, studies in other databases assessing the association between domperidone and SCD or VA are needed. This study emphasizes that it is important for regulatory agencies to add a warning to the product safety information regarding the risk of SCD. For clinicians it is important to avoid prescribing domperidone to patients with a high risk of SCD, e.g. patients already receiving other QTc-prolonging drugs.

In our population, we were able to take advantage of the fact that in the Dutch healthcare system, all medical information (including specialist and hospital care) is collected at GP practices that cover the general population instead of selected socioeconomic groups. Consequently, there was extensive information available on drug use, potential confounders and all the circumstances surrounding death.

Nevertheless, our study has some potential limitations. First, we cannot exclude that some misclassification of outcome occurred. We may have missed some deaths, although this will be minimal since death is consistently registered by GPs. Second, not all acute deaths may have been of cardiac origin. We determined SCD, however, on the basis of the full medical records, and all circumstances surrounding the death were available. Recently, an evaluation comparing different methods to determine the incidence of SCD suggested that this method provides a very reliable way of determining SCD cases.[17] Third, we may have missed some VAs, although this will be minimal due to the broad search criteria we used. All VA cases were determined based on the full medical records, and needed to have an ECG confirmation. We may have missed all cases who died without ECG evidence but these will be included as SCD. Finally, since we only included definite VA cases not preceded by other disease, such as myocardial infarction, misclassification will be minimal.

Misclassification of exposure may have occurred for various reasons. First, we used outpatient prescription data and we had no information as to whether the prescription was actually filled and taken. Second, the legend duration for a calculated prescription (indicating the theoretical duration) may not reflect actual use. However, as in most cases (n = 7) use was not on an as-needed basis, the legend duration probably well matches the actual duration of use. Third, since 1 January 2004, domperidone is no longer reimbursed even when prescribed (from 1 January 2005 reimbursed again in long-term use). Publicly insured persons had a higher prevalence of recorded domperidone use than privately insured patients, but in 2004 the prevalence dropped in publicly insured patients and remained stable in privately insured patients, pointing to differential misclassification by insurance type, which can be seen in figure 1. Since we observed near interaction with insurance we stratified by this variable. Fourth, potential non-continuous use may explain why the risk for SCD was elevated in some past use categories.

Although we adjusted for all known confounders, residual confounding may exist, but it is unlikely that this would explain the strong association for high doses of domperidone. An increased risk with past use would have been consistent with confounding by indication; however, past use was not significantly associated with an increased risk of SCD. Adjustment for GP visits showed an effect as confounder, which may be explained by the fact that prodromal symptoms of SCD, such as nausea and vomiting, can be mistakenly diagnosed as symptoms due to gastric pathology. Diabetic gastropathy was considered to be a potential confounder. However, in patients without diabetes, the association between current use and SCD increased, which excludes

the possibility of residual confounding by diabetic gastropathy. In patients without cardiovascular disease, current use of domperidone was associated with an increased risk, which avoids residual confounding due to the severity of underlying cardiovascular disease.

Conclusions

This study underscores our prior conclusion that domperidone use is associated with an increased risk of SCD;[2] however, it refines it to the extent that mainly high dosages are associated with an increased risk, and it excludes the alternative explanations such as confounding by diabetic gastropathy and protopathic bias. This study was specifically designed to investigate the association between domperidone and VA, and this association could not be demonstrated because of the lack of exposed and few confirmed VA cases.

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The study is an accurate representation of the study results.

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