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In-hospital cardiac arrest is associated with use of non-antiarrhythmic QTc-prolonging drugs

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Aims
QTc interval-prolonging drugs have been linked to cardiac arrhythmias, cardiac arrest and sudden death. In this study we aimed to quantify the risk of cardiac arrest associated with the use of non-antiarrhythmic QTc-prolonging drugs in an academic hospital setting.

Methods
We performed a case–control study in which patients, for whom intervention of the advanced life support resuscitation team was requested for cardiac arrest between 1995 and 2003 in the Academic Medical Centre, Amsterdam, were compared with controls regarding current use of non-antiarrhythmic QTc-prolonging drugs. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression, adjusting for potential confounding factors.

Results
A statistically significant increased risk of cardiac arrest (OR 2.1, 95% CI 1.2, 3.5) was observed in patients who received QTc-prolonging drugs (42/140). The risk was more pronounced in patients receiving doses >1 defined daily dose (OR 2.5, 95% CI 1.1, 5.9), patients taking >1 QTc-prolonging drug simultaneously (OR 4.8, 95% CI 1.6, 14) and patients taking pharmacokinetic interacting drugs concomitantly (OR 4.0, 95% CI 1.2, 13).

Conclusions
Use of non-antiarrhythmic QTc-prolonging drugs in hospitalized patients with several underlying disease is associated with an increased risk of cardiac arrest. The effect is dose related and pharmacokinetic drug–drug interactions increase the risk substantially. Physicians caring for inpatients should be made aware of the fact that these non-antiarrhythmic drugs may be hazardous, so that potential risks can be weighed against treatment benefits and additional cardiac surveillance can be requested, if necessary.

Introduction

A wide range of QTc-prolonging non-antiarrhythmic drugs have been linked to the occurrence of cardiac arrhythmias, especially torsade de pointes [1]. Torsade de pointes is a polymorphic ventricular arrhythmia, which can be self-limiting or degenerate into ventricular fibrillation, cardiac arrest and sudden death [2]. Several population-based epidemiological studies on drug-

induced arrhythmias have indicated that the proarrhythmic risk of non-antiarrhythmic drugs is not very high among the general population [3–6], but can be substantial among subgroups of patients with underlying diseases, such as schizophrenia [6] or asthma [3]. In daily clinical practice, potential proarrhythmic drugs are advised not to be prescribed to patients with pre-existing risk factors [7]. In a hospital setting, however, and particularly a university hospital setting, this may be hard to achieve, since virtually all patients have some underlying disease and treatment with potentially hazardous drugs may be necessary. In this study we aimed to quantify the risk of cardiac arrest associated with the use of non-antiarrhythmic QTc-prolonging drugs in a university hospital setting.

Methods

Setting

This study was conducted at the Academic Medical Centre, Amsterdam, a tertiary care and university teaching hospital (1000 beds, 23 600 admissions per year, mean length of stay 9 days). All patients receiving inhospital care between 1 January 1995 and 25 December 2003 with complete computerized medical records on drug exposure variables and potential confounders were initially eligible for the study.

Design

A case–control study was performed. Cases were defined as patients experiencing circulatory arrest for whom intervention of the advanced life support resuscitation team (including medical doctors in the field of anaesthesiology and cardiology, as well as a Cardiac Care Unit nurse) was requested. Patients in whom the arrest occurred either prior to hospital admission, in the emergency room (ER) or during an outpatient visit were excluded. Per case, four controls from all other patients receiving inhospital care were selected at the date the case was resuscitated (index date).

Exposure definition

Current inhospital exposure to non-antiarrhythmic QTc-prolonging drugs with a clinically relevant proarrhythmic risk (published clinical evidence for torsade de pointes or ventricular arrhythmias) was assessed for cases and controls (see Appendix 1 [1]). A patient was defined as a current user if the index date fell between the prescription date and the end date of the prescription. Exposure was assessed through the automated pharmacy database in which all prescribed medication of patients receiving inhospital care is collected. To ensure knowledge of all currently used drugs and exclude effects of previously used drugs, patients were eligible only if the medication records of the present hospitalization started at least 1 day before the index date.

Among current users we evaluated the effect of dose, measured in defined daily dose equivalents, as defined by the World Health Organization [8]. One defined daily dose equivalent represents the recommended daily dose for an adult (Appendix 1). In order to evaluate dose–response effects, the daily dose of QTc-prolonging drugs was categorized into ≤ 1 defined daily dose and >1 defined daily dose. In addition, the effect of the number of different QTc-prolonging drugs taken simultaneously was assessed. We also evaluated the effect of concomitant medication, which can inhibit the metabolism of the study drugs. Patients that used QTc-prolonging drugs which are metabolized through one of the cytochrome P450 isoenzymes according to Flockheart *et al.* (Appendix 2) [9] were checked for concomitant use of clinically relevant inhibitors of those isoenzymes.

Potential confounders

The association between the use of non-antiarrhythmic QTc-prolonging drugs and cardiac arrest in this hospital-based study may be confounded by secondary factors which were associated with both the exposure and the outcome, such as confounding by indication [10]. We therefore evaluated the influence of age, gender, several comorbidities (cardiac arrhythmias, other cardiac disease, diabetes mellitus, pulmonary disease, hepatic and renal impairment), concomitant use of class I and III antiarrhythmic drugs, total number of currently used drugs and electrolyte disturbances (calcium, magnesium, potassium) on the calculated association.

Data on potential confounders were retrieved from the medical records through computerized searches. Cardiac arrhythmias were defined by hospital discharge diagnosis for the disease (ICD code 427). Antiarrhythmic proarrhythmic drug use was defined as current use of class I or III antiarrhythmic drugs. Other cardiac disease was defined as either a prescription for other cardiac drugs and/or a hospital discharge diagnosis (ICD code) for ischaemic heart disease (410–414), heart failure (428), cardiomyopathy (425), valvulopathy (4240, 4241, 4242, 4243), artificial heart (valve) (V421, V422, V432, V433) and/or a hospital procedure for coronary artery bypass graft (5361, 5362, 5363) or percutaneous transluminal coronary angioplasty (88370, 88378, 88379). Diabetes mellitus was defined as either a prescription for antidiabetic drugs and/or a hospital discharge diagnosis for diabetes (ICD code 250). Pulmonary disease was defined as either a prescription

for antiasthmatic drugs and/or a hospital discharge diagnosis (ICD code) for asthma (493), chronic bronchitis (491) or emphysema (492). Normal serum electrolyte levels, based on the criteria used in the Academic Medical Centre, were defined as calcium between 2.1 and 2.55 mmol l^{-1}, magnesium between 0.7 and 1 mmol l^{-1}, potassium between 3.5 and 5 mmol l^{-1}. Hepatic and renal impairment were defined by an expert panel consisting of an internist and a cardiologist as serum total bilirubin concentrations >50 μmol l^{-1} and serum creatinine concentrations >110 μmol l^{-1} (males) or 100 μmol l^{-1} (females), respectively. Serum concentrations had to be measured during the 7 days previous to the index date. If multiple measurements were taken, the value closest to the index date was used.

Data analysis

The relative risk, estimated by the odds ratio (OR) and 95% confidence interval (CI) of the association between exposure to QTc-prolonging drugs and cardiac arrest, was calculated using unconditional logistic regression analysis. All potential confounders were univariately associated with cardiac arrest (at a $P < 0.1$ level) and included in the multivariate regression analyses. All statistical analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 140 patients were resuscitated for cardiac arrest in the Academic Medical Centre and fulfilled the eligibility criteria. The mean age of cases was significantly higher (59.6 years) than of controls (47.5 years) and cases were more often male than were controls (65.7% *vs*. 48.9%). All known potential risk factors for cardiac arrest were associated with an increased risk, notably cardiac arrhythmias, other cardiac disease, diabetes mellitus, pulmonary disease, electrolyte disturbances and hepatic as well as renal impairment. As expected, the use of antiarrhythmic drugs and the total number of currently used drugs were also associated with cardiac arrest (Table 1). The most pronounced were the associations between cardiac arrhythmias (adjusted OR 6.6, 95% CI 3.7, 12) as well as hyperkalaemia (adjusted OR 4.1, 95% CI 1.6, 10) and cardiac arrest.

Current use of non-antiarrhythmic QTc-prolonging drugs was associated with a twofold increased risk of cardiac arrest (crude OR 1.8, 95% CI 1.2, 2.8). This risk increased slightly after adjustment for confounders (adjusted OR 2.1, 95% CI 1.2, 3.5). The risk of cardiac arrest increased with dose (adjusted OR >1 defined daily dose 2.5, 95% CI 1.1, 5.9) and number of QTc-prolonging drugs taken simultaneously (adjusted OR >1 drug 4.8, 95% CI 1.6, 14) and was twice as high when QTc-prolonging drugs were taken concomitantly with other drugs that inhibit the metabolism (adjusted OR 4.0, 95% CI 1.2, 13). Of the individual drugs, domperidone and haloperidol appeared to have the greatest risks (Table 2).

Discussion

The results of our study indicate that current use of non-antiarrhythmic QTc-prolonging drugs is associated with a doubled risk of cardiac arrest in a hospital setting. From previously published data it is known that QTc-prolonging drugs increase the risk of arrhythmias such as torsade de pointes and sudden death [1, 2]. Furthermore, population-based epidemiological studies indicate that the proarrhythmic risk of these drugs in the general population is not very high [3–6], but can be substantial among subgroups of patients with underlying diseases, such as schizophrenia [6] or asthma [3]. Our most important finding is that these results indicate that the risk of inhospital cardiac arrest is doubled when currently using non-antiarrhythmic QTc-prolonging drugs. This is, to our knowledge, the first report to quantify the inhospital relative risk factor on cardiac arrest, a hard outcome parameter, in this setting.

Although the study was not designed to investigate individual drugs risks, or to study effects in subgroups, it is interesting to see that the risks were highest among patients taking two medications mainly used in palliative care: domperidone and haloperidol. Domperidone is used to treat gastrointestinal discomfort [11]. In a hospital setting haloperidol is mainly used to treat delirium [12]. Both drugs are known for their potential proarrhythmic effects [12, 13] and warnings are included in the Summary of Product Characteristics. Apparently, the potential benefits of treatment outweigh the adverse effects in a clinical setting. Another interesting finding is the fact that the association between non-antiarrhythmic QTc-prolonging drugs and cardiac arrest appears to be greater among the 93 patients with hypokalaemia (adjusted OR 3.3, 95% CI 0.7, 15). Hypokalaemia is one of the main risk factors for drug-induced arrhythmia [14].

The magnitude of the potential problem in a hospital setting such as this is reflected in the fact that almost 20% of the source population is using non-antiarrhythmic QTc-prolonging drugs. This prevalence in much higher than that of exposure to one of the drugs from this same list in the general population, which is about 1% [1].

The number of cases included in our study may seem low in a university hospital for a period of almost 9 years [15]. The total number of cardiac arrests for whom inter-

vention of the advanced life support resuscitation team was requested, in this study period, exceeded 1200. However, almost 50% of the interventions took place in the ER. No information on current medication use could be retrieved through computerized searches in these out-of-hospital cardiac arrest cases. Furthermore, the inclusion of inhospital cardiac arrest cases was relatively low (140/600). This was due to the fact that the hospital was implementing a computerized physician drug order entry system (CPOE) starting in 1996 with two wards and gradually increasing the number of wards until mid 2001. Eventually, all wards used this CPOE with the exception of the ER, operation rooms and intensive care units. Exclusion of inhospital cardiac arrest cases was mainly because not all requested information, especially concerning prescribed drugs, could be retrieved through computerized searches.

A finding consistent with other studies on the association between QTc-prolonging drugs and cardiac arrhythmias is that there appears to be a positive dose–response relationship [3, 6, 16–19]. In accordance with Ray *et al.* [20], we found that cytochrome P450 pharmacokinetic drug–drug interactions apparently play an important role.

The data we used were not recorded for research purposes, but to support medical and pharmaceutical care, to improve medication safety and for administrative reasons. The main advantage of these data is the fact that they were collected prospectively and are unlikely to be subject to differential misclassification [21]. However, we cannot exclude the possibility that some non-differential misclassification of outcome and exposure may have occurred or that some residual confounding may still be present. First, some control patients with a

Table 1
Characteristics of cases and controls

	Cases (n = 140)	(%)	Controls (n = 560)	(%)	χ^2 P-value
Gender female	48	(34.3)	286	(51.1)	< 0.0001
Age (mean, SD)	59.6	(21.7)	47.5	(26.8)	< 0.0001
Drug use					
Non-antiarrhythmic QTc-prolonging drugs	42	(30.0)	107	(19.1)	0.005
Antiarrhythmic QTc-prolonging drugs	13	(9.3)	17	(3.0)	0.001
Total number of current drugs (mean, SD)	9.4	(4.4)	7.5	(4.6)	< 0.0001
Comorbidity					
Cardiac arrhythmias	50	(35.7)	31	(5.5)	< 0.0001
Other cardiac disease	69	(49.3)	110	(19.6)	< 0.0001
Diabetes mellitus	46	(32.9)	68	(12.1)	< 0.0001
Pulmonary disease	41	(29.3)	89	(15.9)	< 0.0001
Serum levels					
K <3.5 mmol l^{-1}	26	(18.6)	67	(12.0)	< 0.0001
K 3.5–5 mmol l^{-1}	86	(61.4)	304	(54.3)	
K >5 mmol l^{-1}	16	(11.4)	15	(2.7)	
K not measured during last week	12	(8.6)	174	(31.1)	
Ca <2.1 mmol l^{-1}	30	(21.4)	40	(7.1)	< 0.0001
Ca 2.1–2.55 mmol l^{-1}	51	(36.4)	106	(18.9)	
Ca >2.55 mmol l^{-1}	2	(1.4)	22	(3.9)	
Ca not measured during last week	57	(40.7)	392	(70.0)	
Mg <0.7 mmol l^{-1}	9	(6.4)	18	(3.2)	0.004
Mg 0.7–1 mmol l^{-1}	14	(10.0)	35	(6.3)	
Mg >1 mmol l^{-1}	5	(3.6)	4	(0.7)	
Mg not measured during last week	112	(80.0)	503	(89.8)	
Bilirubin < 50 μmol l^{-1}	36	(25.7)	97	(17.3)	0.002
Bilirubin > 50 μmol l^{-1}	9	(6.4)	13	(2.3)	
Bilirubin not measured during last week	95	(67.9)	450	(80.4)	
Creatinine < 110 μmol l^{-1} (M),100 μmol l^{-1} (F)	82	(58.6)	303	(54.1)	< 0.0001
Creatinine > 110 μmol l^{-1} (M),100 μmol l^{-1} (F)	50	(35.7)	70	(12.5)	
Creatinine not measured during last week	8	(5.7)	187	(33.4)	

Table 2
Risk of cardiac arrest and non-antiarrhythmic QTc-prolonging medication

Use of QTc-prolonging drugs	Cases (n = 140)	Controls (n = 560)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Non-use	98	453	1 ref	1 ref
Current use	42	107	1.8 (1.2, 2.8)	2.1 (1.2, 3.5)
Daily dose				
Non-use	98	453	1 ref	1 ref
≤1 defined daily dose	28	78	1.7 (1.0, 2.7)	1.9 (1.1, 3.5)
>1 defined daily dose	14	29	2.2 (1.1, 4.4)	2.5 (1.1, 5.9)
Number of QTc-prolonging drugs				
Non-use	98	453	1 ref	1 ref
One drug	33	94	1.6 (1.0, 2.6)	1.8 (1.0, 3.1)
≥2 drugs simultaneously	9	13	3.2 (1.3, 7.7)	4.8 (1.6, 14)
Drug–drug interactions				
Non-use	98	453	1 ref	1 ref
QTc-prolonging drugs only	34	99	1.6 (1.0, 2.5)	1.9 (1.1, 3.2)
QTc-prolonging drugs +P450 inhibitors	8	8	4.6 (1.7, 13)	4.7 (1.3, 16)
Type of QTc-prolonging drug used†				
Non-use	98	453	1 ref	1 ref
Amitriptyline	4	10	1.9 (0.6, 6.0)	2.0 (0.5, 8.1)
Cisapride	6	21	1.3 (0.5, 3.4)	1.3 (0.4, 4.0)
Clarithromycin	3	7	2.0 (0.5, 7.8)	1.4 (0.2, 8.6)
Cotrimoxazole	9	30	1.4 (0.6, 3.0)	2.6 (1.1, 6.4)
Domperidone	7	15	2.2 (0.9, 5.4)	4.7 (1.4, 16)
Haloperidole	15	18	3.9 (1.9, 7.9)	3.8 (1.6, 9.2)
Promethazine	3	13	1.1 (0.3, 3.8)	1.2 (0.3, 5.4)
Other QTc-prolonging drug	4	9	2.1 (0.6, 6.8)	1.3 (0.3, 5.6)

**Adjusted for age, gender, cardiac arrhythmias, other cardiac disease, diabetes mellitus, pulmonary disease, total number of current drugs, concomitant use of antiarrhythmic drugs, serum potassium, calcium, magnesium, creatinine, and bilirubine. †Some patients used >1 QTc-prolonging drug, numbers do not add up.*

do-not-attempt-resuscitation order may have actually experienced cardiac arrest, without intervention of the advanced life support resuscitation team. The proportion of patients with a do-not-attempt-resuscitation order was found to depend on age and comorbidity in the Academic Medical Centre [22]. According to the age distribution, we expect that 57 of the 560 control patients in our study may have had a do-not-attempt-resuscitation order. Assuming that 10% of these patients actually experienced a cardiac arrest implies that only 1% of our control patients were misclassified. This may have resulted in a minor underestimation of the true effect. Second, misclassification of exposure may have occurred, but was minimized, because patients were included only if the medication records of the present hospitalization started at least 1 day before the index date. In addition, it is likely that any such exposure misclassification will be random and will be evenly distributed between cases and controls. Third, we may not have been able to control fully for disease severity. Patients appeared to be more severely ill than controls. This was reflected in the higher number of prescribed drugs, a higher prevalence of comorbidity as well as electrolyte disturbances and the fact that serum levels for electrolytes and renal and hepatic function were measured more often during the week before the index date. We took all these factors into account in our analyses, but were not able to adjust for a standardized measure of disease severity such as the APACHE II score.

Another factor which may have influenced our results is that doctors refrain from prescribing QTc-prolonging drugs to high-risk patients, so-called 'confounding by contraindication' [10]. This may have resulted in an apparently absent association between use of cisapride and cardiac arrest on the one hand and a large association between use of domperidone and cardiac arrest on

the other hand, when physicians prescribe domperidone instead of cisapride in high-risk patients. Cisapride-induced arrhythmias have received much greater attention in recent years than domperidone-induced arrhythmias [13]. This hypothesis is strengthened by the fact that until 2001 cisapride was taken twice as often as domperidone, whereas after 2001 domperidone was taken twice as often as cisapride. The overall awareness of risks associated with prescribing non-antiarrhythmic QTc-prolonging drugs to patients is not very high considering the fact that even in the control population almost one-fifth of the patients were taking these drugs. Since March 2005 physicians and pharmacists have been warned by the hospitals' CPOE when non-antiarrhythmic QTc prolonging drugs are prescribed. It would be interesting to see if the percentage of patients prescribed these classes of drugs will decrease over time due to this alert.

Although we emphasize above the causative factors that explain at least some of our findings, it should be borne in mind that due to the non-experimental, observational design of our research, our findings indicate merely associations and not necessary causal relationships.

In conclusion, the results of our study indicate that current use of non-antiarrhythmic QTc-prolonging drugs in hospitalized patients with several underlying disease is associated with an increased risk of cardiac arrest. The effect is dose related and pharmacokinetic drug–drug interactions increase the observed risk substantially. Hospital specialists should be made aware of the fact that these non-antiarrhythmic drugs may be hazardous, so that potential risks can be weighed up against treatment benefits and additional cardiac surveillance can be requested, if necessary.

Competing interests: None declared.

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Appendix 1

QTc-prolonging drugs having a clinically relevant proarrhythmic risk and defined daily dose (mg) [1]*

Drug	1 DDD	Drug	1 DDD	Drug	1 DDD
GI-prokinetics		*Antipsychotics*		*Antimalarials*	
Cisapride	30	Chlorpromazine	300	Chloroquine	500
Domperidone	30	Droperidol	15	Halofantrine	1500
Cardiovascular		Haloperidol	8	*Antihistamines*	
Indapamide	2.5	Pimozide	4	Astemizole	10
Ketanserin	40	Sultopride	1200	Diphenhydramine/	200
Lidoflazine	180	Thioridazine	300	dimenhydrinate	
Probucol	250	*Antidepressant*		Promethazine	25
Antibacterials		Amitriptyline	75	Terfenadine	120
Clarithromycin	500	Clomipramine	100	*Miscellaneous*	
Erythromycin	1000	Doxepine	100	Pentamidine	280
Grepafloxacin	400	Mianserine	60	Tacrolimus	5
Cotrimoxazole	1920	Protriptyline	30	Terodiline	50
Sulfamethoxazole	2000	Zimeldine	200		
Trimethoprim	400				

**Clinical data do not provide a strong signal for fexofenadine, fluoxetine, clindamycin, levofloxacin, spiramycin and fluconazole [1]. These drugs are excluded from the original selection. DDD, Defined daily dose.*

Appendix 2

Clinically relevant P450 interactions according to Fockhart et al. [9]

Drug	CYP2C19	CYP2C9	CYP2D6	CYP3A4
Substrate				
Amitriptyline	X		X	
Astemizole				X
Cisapride				X
Clarithromycin				X
Clomipramine	X		X	
Erythromycin				X
Haloperidol			X	X
Pimozide				X
Sulfamethoxazole		X		
Tacrolimus				X
Terfenadine				X
Thioridazine			X	
Inhibitor				
Amiodarone		X	X	X
Chlorpheniramine			X	
Cimetidine			X	X
Clarithromycin				X
Clomipramine			X	
Diltiazem				X
Erythromycin				X
Fluconazole		X		
Fluoxetine	X		X	X
Fluvoxamine	X			X
Haloperidol			X	
Indinavir				X
Isoniazid		X		
Itraconazole				X
Ketoconazole	X			X
Lansoprazole	X			
Methadone			X	
Mibefradil			X	X
Nefazodone				X
Nelfinavir				X
Omeprazole	X			
Paroxetine			X	
Quinidine			X	
Ritonavir			X	X
Saquinavir				X
Ticlopidine	X	X		
Troleandomycin				X
Verapamil				X

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