Use of selective serotonin reuptake inhibitors and risk of developing first-time acute myocardial infarction

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Aims Selective serotonin reuptake inhibitors (SSRIs) have been associated with serotonin depletion in platelets, potentially leading to abnormal aggregation and prolonged bleeding time. In view of the importance of serotonin in coronary thrombosis, and decreased platelet serotonin concentrations associated with SSRIs, the present study was performed to test the hypothesis of a decreased risk of acute myocardial infarction (AMI) associated with SSRIs.

Methods We conducted a population-based case-control analysis using the UK General Practice Research Database (GPRD). A total of 3319 patients aged 75 years or younger free of clinical conditions predisposing to ischaemic heart disease, with a first-time diagnosis of AMI between 1992 and 1997, and 13 139 controls without AMI matched to cases for age, sex, general practice attended, and calendar time were included. Conditional logistic regression was used to estimate relative risks.

Results Adjusted odds ratios (with 95% CI) for current use of SSRIs, non-SSRIs, or other antidepressants, compared to the group of nonusers of antidepressants were 0.9 (95% CI 0.5,1.8), 0.9 (95% CI 0.7,1.2), and 1.3 (95% CI 0.6,2.8), respectively. As compared with nonuse of SSRIs, current use (regardless of any other antidepressants used) resulted in an adjusted OR of 1.1 (95% CI 0.7,1.6).

Conclusions The current analysis provides evidence that SSRI exposure does not substantially decrease the risk of developing first-time AMI in patients free of factors predisposing to ischaemic heart disease. However, due to relatively small numbers of exposed subjects and the resulting wide confidence intervals, further studies may be needed to document a lack of effect of SSRIs in subjects without pre-existing diseases predisposing to AMI.

Keywords: antidepressive agents, case-control study, epidemiology, myocardial infarction, serotonin uptake inhibitors, serotonin

Introduction

It has been suggested that serotonin promotes thrombogenesis by enhancing platelet aggregation [1]. On the other hand, drugs affecting neuronal serotonin (5-hydroxytryptamine, 5-HT) reuptake are important for the pharmacotherapy of a variety of psychiatric illnesses such as depression, anxiety, panic, social phobia, obsessive-compulsive or eating disorders. Particularly, selective serotonin reuptake inhibitors (SSRIs) are widely used for these indications because of their efficacy, and their relative safety in overdose [2].

It has been shown that SSRIs not only affect neuronal serotonin uptake, but additionally modulate peripheral serotonin. Fluvoxamine, fluoxetine, sertraline and paroxetine reduce platelet and whole blood serotonin concentrations after repeated doses [3-6]. Serotonin is a relatively weak platelet activator on its own. However, in the presence of other proaggregatory factors (e.g. adenosine diphosphate, adrenaline, collagen), serotonin significantly potentiates platelet aggregation [7].

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Several case reports have been published associating use of SSRIs with abnormal platelet aggregation and various bleeding disorders [8–14]. Furthermore, a recent case-control study provided evidence for an increased risk of upper gastrointestinal bleeding associated with SSRI use [15].

In view of the importance of serotonin in coronary thrombosis and the decrease in platelet serotonin concentrations associated with SSRIs, we studied the association of SSRIs exposure and the risk of developing AMI.

Methods

Study population and data source

Data were derived from the United Kingdom-based General Practice Research Database (GPRD), which has been previously described in detail elsewhere [16-18]. Since 1987, more than 3 million residents in the UK have been enrolled by selected general practitioners who have agreed to provide data for research purposes to the GPRD. The age and sex distribution of the patients enrolled is representative of the entire UK-population. Furthermore, the information recorded includes patient demographics and characteristics (e.g. height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, hospital admissions, and drug prescriptions, including the specific preparation, route of administration, dose, and number of tablets for each prescription. On request, hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record. The GPRD currently encompasses some 30 million person-years of follow-up; it has been the source for numerous epidemiological studies in recent years, and the accuracy and completeness of these data have been well documented and validated [17, 19, 20]. GPRD data have been used in several recent studies investigating risk factors for AMI [21-24] or adverse effects of antidepressants including SSRIs [15, 25–27].

Case definition and ascertainment

Potential cases were selected on the basis of a first-time diagnosis of AMI (by computer-recorded *International Classification of Diseases, Eighth Revision [ICD-8]* codes mapped onto Oxford Medical Information System [OXMIS] codes) between January 1, 1992, and October 31, 1997. We restricted the study to patients who were ≤ 75 years of age at the time of the diagnosis of AMI (index date), and who were free of metabolic or cardiovascular conditions predisposing to AMI. Hence, all patients with a history of AMI, angina pectoris, unexplained chest pain, cardiac dysrhythmias, congestive heart failure, stroke, intermittent claudication, venous thromboembolism, chronic renal disease, hypertension, hyperlipidaemia, diabetes mellitus, or connective-tissue disorders more than 60 days before the AMI were excluded. All cases had to be registered on the database for at least 3 years before the index date. Any information with regard to exposure to antidepressant agents was concealed when the records were reviewed to identify potential cases.

In previous studies using GPRD data [21–24], the computer-recorded diagnosis of a first AMI was validated for a random sample of approximately 450 patients by reviewing hospital discharge letters. A high percentage of computer-identified cases ($>90\%$) were confirmed by at least two of the following documented diagnostic criteria: Characteristic chest pain, characteristic changes in the electrocardiogram, characteristic serial rises in the concentrations of cardiac enzymes, an arteriogram documenting a recent coronary occlusion, or fibrinolytic therapy. Therefore, we decided to include all the potential cases that we identified through a manual review of computerized patient records.

Controls

To estimate the risk of developing a first-time AMI in relation to antidepressant use, we conducted a case-control analysis. Four controls were matched to each case on age (same year of birth), sex, the practice attended, and calendar time by using the same index date for matched controls as for cases. The same exclusion criteria were applied to controls as to cases (i.e. recorded history on the GPRD of less than 3 years, circulatory or metabolic diseases predisposing for AMI >60 days before the index date).

Exposure definition

For each case and control, we assessed the exposure history for antidepressants. Antidepressants were classified in three groups according to their inhibitory capacity on serotonin reuptake [28, 29]: (a) 'selective serotonin reuptake inhibitors' (SSRIs; i.e. citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine); (b) 'nonselective serotonin reuptake inhibitors' (non-SSRIs; i.e. amitriptyline, clomipramine, dothiepin, doxepine, imipramine, lofepramine, nefazodone, trazodone, trimipramine); (c) a miscellaneous group of 'others' (i.e. amoxapine, desipramine, lithium, maprotiline, mianserin, moclobemide, nortriptyline, protriptyline).

A patient was defined as a 'current user' if the supply of the last prescription for an antidepressant prior to the index date lasted until the index date or ended within a period of 30 days prior to the index date. Subjects were defined as

'recent users' when the supply ended between 31 and 60 days prior to the index date, as 'past users' when the supply ended 61 or more days prior to the index date, or as 'nonusers' if no prescription was ever recorded in the medical chart before the index date. Users were further divided into 'single users' and 'mixed users'. The latter category included patients who received prescriptions for different antidepressants (switchers or concomitant use of various antidepressants).

A possible duration or dose effect (according to number of prescriptions or lower *vs* higher daily doses) was studied among current users of SSRIs.

Statistical analysis

We conducted a matched analysis (conditional logistic regression model) using the software program SAS, Version 6.12 (SAS Institute Inc., Cary, NC). Relative risk estimates (odds ratios, OR) are presented with 95% confidence intervals (95% CI), *P* values are two-sided.

For each case and control, the potential confounders body mass index (BMI) (<25, 25–29.9, ≥ 30 kg m^{-2}, unknown), smoking status (never, ex, current, unknown), aspirin use (current *vs* nonuse), hormone replacement therapy, use of antibiotics [24], current upper respiratory tract infection [23], and number of GP visits prior to the index date were assessed from the patient profiles. By doing stratified regression analyses, we further evaluated potential effect modification by age (<65 years, ≥ 65 years) and gender.

Results

Overall, we included 3315 cases with AMI and 13 139 controls in the analysis (Table 1). The relative risk estimates (odds ratios, OR) of developing a first-time AMI in relation to antidepressant use adjusted for smoking and BMI are shown in Table 2. The adjusted ORs of current single use of SSRIs, non-SSRIs and other antidepressants, compared with the reference group of nonusers of any antidepressant, were 0.9 (95% CI 0.5,1.8), 0.9 (95% CI 0.7,1.2), and 1.3 (95% CI 0.6,2.8), respectively.

Because use of non-SSRIs and of other antidepressants had no apparent effect on the risk of developing AMI, they were combined with the reference group of nonusers for further analyses to gain additional statistical power. Thus, patients of the mixed group who also had exposure to SSRIs were thereby categorized as SSRI users. The adjusted OR of current, recent and past use of SSRIs, compared with nonusers of antidepressants and users of non-SSRIs or other antidepressants combined, were 1.1 (95% CI 0.7,1.6), 0.6 (95% CI 0.2,1.9), and 1.1 (95% CI 0.9,1.5), respectively (Table 3). Additional subanalyses of SSRI use stratified by age (i.e. <65 years and ≥ 65 years) or gender showed no evidence for effect modification.

Table 1 Characteristics of cases and controls in relation to risk of developing acute myocardial infarction (AMI).

Characteristics	*Cases, Number (%)* (n = *3315*)	*Controls, Number (%)* (n = *13 139*)	*Odds ratio (95% Confidence Interval)*
Age (years)			
<40	91 (2.8)	367 (2.8)	
40–49	417 (12.6)	1656 (12.6)	
50–59	830 (25.0)	3314 (25.2)	
60–69	1227 (37.0)	4832 (36.8)	
70–75	750 (22.6)	2970 (22.6)	
Sex			
Male	2452 (74)	9715 (74)	
Female	863 (26)	3424 (26)	
Smoking status			
Non-smoker	1079 (32.6)	6204 (47.2)	1.0 (Referent)
Current smoker	1100 (33.2)	2574 (19.6)	2.6 (2.3, 2.8)†
Ex-smoker	376 (11.3)	1353 (10.3)	1.6 (1.4, 1.9)†
Body mass index (kg m^{-2})			
<25	885 (26.7)	4240 (32.3)	1.0 (Referent)
25–29	1100 (33.2)	4004 (30.5)	1.3 (1.2, 1.5)†
≥30	387 (11.7)	1208 (9.2)	1.5 (1.4, 1.8)†
Unknown	943 (28.4)	3687 (28.0)	1.2 (1.1, 1.4)†
Died due to AMI*	467 (14.1)	–	

*autopsy finding (patient did not reach the hospital alive).
†$P<0.001$.

Table 2 Risk of first-time acute myocardial infarction associated with the use of antidepressants.

Antidepressant use	*Cases (n = 3315)*	*Controls (n = 13 139)*	*Adjusted* odds ratio (95% Confidence Interval)*
Non-use	2853	11 507	1.0 (Referent)
SSRI† use			
Current	13	51	0.9 (0.5–1.8)
Recent past	2	8	1.0 (0.2–4.7)
Past	32	115	1.0 (0.7–1.5)
Non-SSRI use			
Current	85	333	0.9 (0.7–1.2)
Recent past	8	27	1.2 (0.6–2.7)
Past	230	776	1.2 (1.0–1.3)
Others			
Current	8	26	1.3 (0.6–2.8)
Recent past	0	3	–
Past	5	32	0.6 (0.2–1.5)
Mixed	79	261	1.1 (0.9–1.5)

*adjusted for smoking status and body mass index.
†SSRI indicates selective serotonin reuptake inhibitor.

Table 3 Risk of first-time acute myocardial infarction associated with the use of selective serotonin reuptake inhibitors (SSRI).

Antidepressant use	*Cases (n = 3315)*	*Controls (n = 13 139)*	*Adjusted* odds ratio (95% Confidence Interval)*
Non-use†	3197	12 747	1.0 (Referent)
SSRI use‡			
Current	34	114	1.1 (0.7–1.6)
Recent past	4	21	0.6 (0.2–1.9)
Past	80	257	1.1 (0.9–1.5)

adjusted for smoking status and body mass index.
†Because 'non-SSRIs' and 'other antidepressants' had no apparent effect, they were combined with the reference group of nonusers.
‡Patients of the former 'mixed group' who also had exposure to SSRIs were categorized as SSRI users.

Table 4 Risk of first-time acute myocardial infarction associated with current use of selective serotonin reuptake inhibitors (SSRI) stratified by duration and daily dose.

Antidepressant use	*Cases (n = 3315)*	*Controls (n = 13 139)*	*Adjusted* odds ratio (95% Confidence Interval)*
Non-use	3197	12 747	1.0 (Referent)
SSRI current users			
Duration of use†			
1–3	11	35	1.3 (0.6–2.5)
4–9	7	24	1.2 (0.5–2.8)
≥10	16	55	1.0 (0.5–1.7)
Dose			
Low dose‡	24	87	1.0 (0.6–1.6)
High dose§	10	27	1.3 (0.6–2.8)

*adjusted for smoking status and body mass index.
†expressed as number of prescriptions.
‡low dose: fluoxetine ≤20 mg, fluvoxamine ≤50 mg, paroxetine ≤30 mg, sertraline ≤50 mg, citalopram ≤20 mg, venlafaxine ≤ 75 mg.
§high dose: fluoxetine >20 mg, fluvoxamine >50 mg, paroxetine >30 mg, sertraline >50 mg, citalopram >20 mg, venlafaxine >75 mg.

Furthermore, adjusting the analysis for the potential confounders aspirin use, longer-term use of hormone replacement therapy, the presence of respiratory tract infections at the index date, use of antibiotics, or number of GP visits as a marker for medical attention received, did not materially affect the results. An analysis of current SSRI use stratified according to duration of use (by number of prescriptions, i.e. 1–3, 4–9, ≥10) showed no effect of exposure duration on the risk of developing AMI. Stratification of current SSRI use according to daily dose did not reveal any risk modifying effect of SSRI dose on developing AMI (Table 4).

To take depression itself into consideration as a potential risk factor for AMI, a direct comparison of subjects currently treated with SSRIs with subjects currently treated with non-SSRIs (reference group) was performed. This analysis yielded an adjusted OR of 1.0 (95% CI 0.5,2.0).

Discussion

The findings of this case-control analysis are not compatible with the hypothesis of a materially decreased risk of first-time AMI in current users of SSRIs. We found no difference between cases and controls with regard to exposure timing of the most recent antidepressant used (current, recent or past exposure) or exposure category (SSRIs, non-SSRIs or other antidepressants) prior to the index date. Thus, any potential effect of SSRIs on platelet serotonin did not seem to affect the risk of developing acute coronary thrombosis *in vivo* in this study population. Since decrease of serotonin platelet concentration may occur only after longer-term administration, we further explored whether exposure duration affects the risk of developing AMI. The stratification of current SSRI users by exposure duration did not suggest any relevant influence of previous exposure duration to SSRIs on the risk estimates.

Several studies have shown that both depression and anxiety are independent risk factors for coronary artery disease including AMI [30–34], while other studies have found no association [35, 36]. Patients treated with SSRIs are probably mainly depressed, while other conditions often treated with SSRIs (e.g. eating disorders) are not that common in this study population. In contrast, nonusers of

antidepressants are more likely to be free of diagnosed depression, at least relative to the group of SSRI users. In the absence of a protective effect, patients on SSRIs would be expected to have a higher AMI rate that nonusers. Therefore, the absence of an increased AMI risk among users might be due to an actual decrease in risk relative to what would have been observed in depressed patients if they had not been treated with SSRIs. In addition to studying the effect of SSRIs on the risk of developing first-time AMI, we also explored whether there is an association between exposure to non-SSRIs or other antidepressants and AMI. By comparing various groups of antidepressants with nonusers of antidepressants, we have taken into account that depression itself may be a risk factor for AMI and that exposed subjects may be at a higher risk for AMI due to the underlying condition. However, there was no evidence for an altered AMI risk for any group of antidepressants. In an attempt to take possible confounding by indication into account, we compared current SSRI users with users of non-SSRIs as a reference group, assuming that most patients were described SSRIs or non-SSRIs for depressive disorders. This analysis yielded no difference between patients using SSRIs or non-SSRIs with regard to AMI risk.

We studied first-time AMI cases and matched control subjects without history of diagnosed cardiovascular or metabolic diseases prior to the index date because the effect of newly hypothesized parameters on the risk of developing an outcome in an epidemiological investigation can best be studied in idiopathic cases who were at relatively low *a priori* risk of developing the disease of interest [37]. Furthermore, by excluding subjects with a history of ischaemic heart disease and related cardiovascular or metabolic diseases, we reduced the risk of potential prescribing bias of antidepressant agents by physicians. It has been suggested that SSRIs are less cardiotoxic and proarrhythmogenic compared with tricyclic antidepressants [38–40] and thus may be preferable to tricyclic antidepressants for treatment of depression in patients at risk for cardiac events [4, 38, 41, 42].

The restriction of our analysis to subjects who were free of diagnosed and recorded clinical risk factors for AMI prior to the index date does not necessarily allow to extrapolate the null finding to subjects at high risk of developing AMI due to pre-existing cardiovascular or metabolic diseases. Thus, further studies may be needed to document the lack of effect of SSRI exposure on the risk of developing AMI in subjects with pre-existing diseases prediposing to AMI and to explore possible effect modification by various clinical conditions.

The number of exposed cases in our analysis, especially in the group of SSRI users, is relatively small. Therefore, despite the large study population, the 95% confidence intervals of the relative risk estimates do not entirely exclude a reduced (or increased) risk of developing AMI for current users of SSRIs. Therefore, to increase the statistical precision, even larger studies would be warranted. Another limitation of our study is the lack of information with regard to socio-economic status or exercise, data which are not available on the GPRD. However, it seems unlikely that socio-economic status or exercise are associated with a substantial prescribing bias and preferential prescribing of one antidepressant drug class over another. Furthermore, as with observational studies in general, we cannot completely rule out unknown biases or confounders as possible causes for the null finding of this analysis, despite the high validity of the data system used and the fact that we controlled for a variety of possible confounders. Our results were adjusted for age, sex, geography and calendar time (by matching cases to controls) as well as for smoking status and body mass index (by adjusting the multivariate analysis). Additionally, we were in a position to evaluate the effects of timing, duration and dosing of antidepressant use. The information about timing of exposure (current, recent or past use) is particularly important to explore whether current use of SSRIs affects the risk of developing AMI.

In conclusion, the findings of this large population-based case-control analysis provide evidence that SSRI exposure is not associated with a relevantly altered risk of developing first-time AMI in subjects free of chronic cardiovascular or metabolic diseases predisposing for AMI.

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