Intracranial haemorrhage and use of selective serotonin reuptake inhibitors

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Aims In the past few years an increasing number of bleeding disorders have been reported in association with the use of selective serotonin reuptake inhibitors (SSRIs), including serious cases of intracranial haemorrhage, raising concerns about the safety of this class of drugs. The present study was performed to test the hypothesis of an increased risk of intracranial haemorrhage associated with the use of SSRIs.

Methods We carried out a case-control study nested in a cohort of antidepressants users with the UK-based General Practice Research Database (GPRD) as the primary source of information. The study cohort encompassed subjects aged between 18 and 79 years who received a first-time prescription for any antidepressant from January, 1990 to October, 1997. Patients with presenting conditions or treatments that could be associated with an increased risk of intracranial haemorrhage were excluded from the cohort. Patients were followed-up until the occurrence of an idiopathic intracranial haemorrhage. Up to four controls per case, matched on age, sex, calendar time and practice were randomly selected from the study cohort. We estimated adjusted odds ratios and 95% confidence intervals of intracranial haemorrhage with current use of SSRIs and other antidepressants as compared with nonuse using conditional logistic regression.

Results We identified 65 cases of idiopathic intracranial haemorrhage and 254 matched controls. Current exposure to SSRIs was ascertained in 7 cases (10.8%) and 24 controls (9.7%) resulting in an adjusted OR (95%CI) of 0.8 (0.3,2.3). The estimate for 'other antidepressants' was 0.7 (0.3,1.6). The effect measures were not modified by gender or age. No effect related to dose or treatment duration was detected. The risk estimates did not change according to the location of bleeding (intracerebral or subarachnoid).

Conclusions Our results are not compatible with a major increased risk of intracranial haemorrhage among users of SSRIs or other antidepressants at large. However, smaller but still relevant increased risks cannot be ruled out.

Keywords: intracranial haemorrhage, selective serotonin reuptake inhibitors, serotonin

Introduction

Evidence is accumulating on the increased risk of bleeding associated with the use of selective serotonin reuptake inhibitors (SSRIs) [1–7]. Up to July 1998, the database of the WHO International Drug Surveillance Program

included a total of 3512 cases of bleeding reported in association with this class of drugs [8]. Most were mild disorders like bruising, petechiae, epistaxis and genitourinary bleeding, but a number of serious cases of gastrointestinal bleeding and cerebral haemorrhage, some resulting in a fatal outcome, has been reported, raising concerns about the safety of these drugs.

Formal epidemiological data are, however, scarce. Recently, we confirmed in a population-based case-control study that SSRIs increased the risk of upper gastrointestinal bleeding [9], suggesting that it could be a class effect linked to a blocking effect on the serotonin

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reuptake mechanism in platelets. The present study was carried out to test whether the use of SSRIs is associated with an increased risk of intracranial haemorrhage.

Methods

The primary source of information for this study was the UK-based General Practice Research Database (GPRD) that has been described elsewhere [10]. The information recorded includes demographics, all medical diagnoses, referrals to consultant and Hospital, and all prescriptions issued.

Subjects

We performed a case-control study nested in a cohort of antidepressant users. The study cohort was made up of subjects aged between 18 and 79 years who received a first-time prescription (start date) for any of the study drugs from January 1, 1990 to October 31, 1997. Subjects were excluded if they had a past history of intracranial haemorrhage or a diagnosis of any of the following diseases: ischaemic cerebrovascular disease (including transient ischaemic attack), ischaemic heart disease, heart failure, cardiac dysrhythmia, hyperthyroidism, diabetes, epilepsy, cancer, coagulopathy, chronic liver disease, connective tissue disorders or alcohol abuse. Additionally, patients on anticoagulant therapy and women pregnant during the follow-up were excluded. Patients were followed from the start date until the first of the following occurred: a first-time diagnosis of intracranial (subarachnoid, intracerebral or subdural) haemorrhage, age of 80 years, death or end of the study period. Only idiopathic cases (e.g. those without a primary documented cause such as crano-encephalic trauma, aneurysm, A-V malformation, or thrombocytopaenia) referred to a consultant, admitted to a hospital or resulting in death, qualified for being included in the study.

The computer files of all possible cases, with drug exposure removed, were manually reviewed to confirm their eligibility. Finally, clinical records or death certificates of all potential cases with insufficient information in the computer profile were requested from GPs for validation. The date of first diagnosis was considered the index date for cases and their matched controls.

Up to four controls per case, matched on age (up to ± 5 years), sex, calendar time (the index date of cases) and practice were randomly selected from the base population that gave rise to the cases. The same exclusion criteria used for cases were also applied to controls.

Exposure definition and covariates

A person was defined as 'current user' when the supply of a

prescription for any antidepressant lasted until index date or ended within the 30 days prior to the index date. 'Recent users' were defined as those for whom the supply ended between 31 and 60 days before the index date. The remaining subjects were considered as 'non users'. A sensitivity analysis using a time window of 15 days for current users was done but results did not materially change.

The effect of dose was studied among current users. Duration of use was defined by the number of consecutive prescriptions among current users. Two prescriptions of an antidepressant were regarded as consecutive if they were written less than 61 days apart.

Antidepressants were classified in two groups: (a) 'selective serotonin reuptake inhibitors (SSRI)' which includes fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, clomipramine and trazodone [11–12]; and (b) 'other antidepressants' which mainly includes tricyclic antidepressants (MAO inhibitors were not included).

The following covariates were studied as potential confounders: the presence of a diagnosis of hypertension, migraine, asthma or COPD, smoking status (non-, ex-, current smoker, or unknown), BMI (< 25 , 25 – 29 , $30 + \text{kg m}^{-2}$, or unknown) and current use of NSAIDs, including aspirin (when a prescription was ordered within the 60 day period before the index date).

Analysis

We computed adjusted estimates of the odds ratio (OR) and 95% confidence intervals of intracranial haemorrhage with current use of SSRIs and other antidepressants as compared to nonuse with conditional logistic regression. A separate analysis according to the type of haemorrhage was also carried out. Stratified analysis by age (< 51 , and > 50 years old) and gender was done in order to study if these variables modify the measure of association between antidepressant use and intracranial haemorrhage.

Results

We identified 120 potential cases, 65 of whom were confirmed as cases of idiopathic intracranial haemorrhage (29 intracerebral, 30 subarachnoid, 3 subdural and 3 intracranial without further specification). The reasons for the 55 exclusions were as follows: presence of an aneurysm/AV malformation (14), head injury within the previous 3 months before index date (8), other causes for intracranial bleeding/exclusion criteria (3), diagnosis not confirmed (11), records or death certificates not available (19). Seventy-five percent of cases were women and the mean age was 59 years (s.d., ± 13). A matched control series of 247 subjects was then identified from the study cohort (mean age ($\pm$ s.d.) = 58 ± 13 years; women: 79%). Current exposure

to SSRIs was ascertained in 7 cases (10.8%) and 24 controls (9.7%) yielding an adjusted odds ratio of 0.8 (95%CI, 0.3,2.3) (Table 1). Similar estimates were obtained with other antidepressants (OR = 0.7; 95%CI, 0.3,1.6). Among covariates, current smoking was the only one presenting a significant association (OR = 3.7; 95%CI, 1.7,8.1). The effect measures were not modified by gender or age (data not shown). We did not observe any effect related to dose or treatment duration (Table 2).

The estimates of odds ratio for antidepressants did not change according to the location of bleeding. The ORs (95%CI) of intracerebral haemorrhage associated with the use of SSRIs and other antidepressants were 0.8 (0.1,5.6) and 1.0 (0.2,4.9), respectively. For subarachnoid haemorrhage the ORs were 0.8 (0.2,3.2) and 0.7 (0.2,2.8), respectively. Among covariates, the record of a diagnosis of hypertension (RR = 3.8; 95%CI, 1.0,14.5), current smoking (RR = 5.9, 95%CI, 1.2,28.1), a body mass index over 30 kgm⁻² (RR = 7.6, 95%CI, 1.1,55.3) and current use of NSAIDs (RR = 4.3, 95%CI, 1.0,19.1) showed an association with an increased risk of intracerebral bleeding (Table 3), while only current smoking (RR = 3.6; 95%CI, 1.1,12.3) was associated with an increased risk of subarachnoid haemorrhage.

Discussion

The results of the present study are not compatible with a major increased risk of intracranial bleeding associated with the use of SSRIs or antidepressants in general. However, the statistical power was insufficient to rule out small but still relevant increased risks. Neither the variation on dose nor the duration of treatment showed any influence. The estimates did not change with the type of intracranial haemorrhage.

Serotonin is known to play a role in platelet aggregation

Table 1 Risk of intracranial haemorrhage associated with the use of antidepressants for all cases combined.

	Cases (n = 65)	Controls (n = 247)	Adjusted* Odds ratio (95% CI)
Non use	44	160	1 (reference)
Current use**			
SSRI	7	24	0.9 (0.4,2.4)
Other antidepressants	11	51	0.8 (0.4,1.6)
Recent use	3	12	0.8 (0.2,3.1)

*Adjusted for age, sex, calendar time and practice (the adjustment for hypertension, smoking, body mass index, asthma/COPD, migraine and NSAID use did not change the estimates) **Two subjects (one case and one control) used two different antidepressants within the 30 days period prior to the index date, and were classified according to the last antidepressant prescribed.

Table 2 Effect of dose and treatment duration among current users as compared with non use.

	Cases (n = 65)	Controls (n = 247)	Adjusted* odds ratio (95% CI)
<i>Duration of treatment (number of prescriptions)</i>			
SSRIs 1–2	4	8	1.6 (0.4,5.6)
3	3	16	0.6 (0.2,2.2)
Others 1–2	6	19	1.1 (0.4,3.0)
3	5	32	0.6 (0.2,1.5)
<i>Daily doses</i>			
SSRIs Low-medium†	4	12	1.1 (0.3,3.8)
High	3	12	0.6 (0.1,3.0)
Others Low-medium‡	10	39	0.9 (0.4,2.0)
High	1	12	0.3 (0.0,2.4)

*Adjusted for age, sex, calendar time and practice (the adjustment for hypertension, smoking, body mass index, asthma/COPD, migraine and NSAID use did not change the estimates). †Fluoxetine: ≤ 20 mg; fluvoxamine: ≤ 100 mg; paroxetine: ≤ 20 mg; sertraline: ≤ 50 mg; citalopram: ≤ 20 mg; clomipramine: ≤ 75 mg; trazodone: ≤ 125 mg; ‡Amitriptyline: ≤ 75 mg; dothiepin: ≤ 75 mg; imipramine: ≤ 75 mg; doxepin: ≤ 75 mg; lofepramine: ≤ 140 mg.

[13, 14]. Platelets capture this amine from circulation through an identical mechanism to the one used by neurones [15], and SSRIs block this reuptake resulting in a depletion of platelet serotonin after several weeks of treatment [16]. It has been postulated that this effect may lead, in certain subjects, to an impairment of haemostatic function, increasing the risk of bleeding. Other authors have postulated that the resulting hyperserotoninaemia may also contribute by increasing vascular fragility [2, 17]. Multiple case reports of bruising and petechiae, some of them with a positive re-exposure, and some accompanied with an increase in bleeding time, have suggested a causal relationship [1, 3, 18]. More convincing evidence has recently come from a population-based case-control study showing a three-fold increase in the risk of upper gastrointestinal bleeding and a strong interaction with NSAIDs [9]. The results of the present study seem to be inconsistent with this body of evidence. However, local factors, such as inadvertent trauma in the case of bruising, or the presence of mucosal aggressors in the case of UGIB, may play an important role. An impairment in platelet aggregation may not suffice to increase the risk of intracranial bleeding by itself. In a recent study, it has been shown that aspirin at low-doses did not increase the risk of intracerebral bleeding [19], while it is well known that at such doses aspirin produces a relevant anti-platelet effect [20] resulting in a small increased risk of gastrointestinal bleeding [21].

Our study was, however, sensitive enough to detect the effect of three well-known cardiovascular risk factors on intracerebral haemorrhage: hypertension, smoking, and

Table 3 Risk of intracerebral haemorrhage associated with the use of antidepressants.

	Cases (n = 29)	Controls (n = 114)	Adjusted* odds ratio (95% CI)
<i>Antidepressant use</i>			
Non use	19	76	1 (reference)
Current use			
SSRI	3	9	0.8 (0.1,5.6)
Other antidepressants	5	21	1.0 (0.2,4.9)
Recent use	2	5	0.5 (0.0,15.8)
<i>Hypertension</i>	10	19	3.8 (1.0,14.5)
<i>Smoking</i>			
Never	9	64	1 (reference)
Current	13	22	5.9 (1.2,28.1)
Ex-smoker	1	7	3.0 (0.2,54.3)
Unknown	6	18	1.3 (0.2,7.2)
<i>Body mass index</i>			
<25	7	48	1 (reference)
25-29	2	38	0.6 (0.1,3.7)
30+	7	9	7.6 (1.1,55.3)
Unknown	13	16	7.7 (1.4,41.7)
<i>Asthma/COPD</i>	7	12	2.9 (0.6,12.5)
<i>Migraine</i>	2	9	3.2 (0.3,29.6)
<i>NSAID use</i>	7	10	4.3 (1.0, 19.1)

*Adjusted for age, sex, calendar time and practice in addition to the factors described.

overweight. The association observed with NSAIDs should be interpreted with caution due to the small numbers.

As with other observational studies, the present one may have been affected by bias and confounding. However, we consider it unlikely that any of the potential biases can satisfactorily explain our results. In contrast to traditional case-control studies, in the current study recall bias cannot effect drug exposure because all prescriptions are routinely recorded in the computer. Most cases were validated through paper-based clinical records or death certificates minimizing the misclassification of outcomes. A diagnosis or referral bias is highly unlikely due to the seriousness of the clinical events in question. Finally, we tried to control for a number of potential confounding factors, but the possibility still exists for residual confounding as a result of unmeasured or inaccurately measured risk factors.

In conclusion, we did not identify any meaningful increase in risk of intracranial haemorrhage in the population of antidepressant users at large. Whether special subgroups might present an increased risk should be investigated further.

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