Antihypertensive drugs and the risk of idiopathic aplastic anaemia

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Aims A recent report has raised concern that nifedipine may be associated with an increased risk of aplastic anaemia. This large population-based study evaluated the risk of idiopathic aplastic anaemia in users of calcium channel blockers compared with that of other antihypertensive drugs.

Methods The study was based on information derived from the General Practice Research Database. We conducted a follow-up study with a nested case-control analysis of 322 448 subjects who received antihypertensive drugs. Cases were people who had a first-time diagnosis of aplastic anaemia during January 1, 1988 through September 30, 1997. The risk estimate of aplastic anaemia was calculated for all antihypertensive drugs. For the nested case-control analysis, six controls were matched to each case on age, sex and general practice attended. Odds ratios compared the risk of idiopathic aplastic anaemia for all antihypertensive drugs relative to nonusers.

Results There were 13 cases of newly diagnosed idiopathic aplastic anaemia. The estimated risk of aplastic anaemia per 100 000 users was 0.8 (95% CI 0.1, 4.7) for calcium channel blockers, 1.4 (95% CI 0.5, 4.1) for β-adrenoceptor blockers, 2.3 (95% CI 0.6, 8.6) for angiotension-converting enzyme (ACE) inhibitors and 5.9 (95% CI 1.6, 21.5) for users of other antihypertensive drugs. In the case-control analysis of 13 cases and 77 controls, the odds ratio was 0.3 (95% CI 0.02, 3.3) for calcium channel blockers, 0.5 (95% CI 0.1, 2.5) for β-adrenoceptor blockers, 0.7 (95% CI 0.1, 5.6) for ACE inhibitors, 1.2 (95% CI 0.1, 11.8) for users of other antihypertensive drugs and 0.7 (95% CI 0.1, 7.2) for users of multiple drugs with a calcium channel blocker compared with nonusers.

Conclusions The present study suggests that the use of calcium channel blockers is not associated with an increased risk of aplastic anaemia.

Keywords: aplastic anaemia, calcium channel blockers, nifedipine

Introduction

Aplastic anaemia is a rare illness. Causes of aplastic anaemia include radiation, viruses, organic compounds and certain drugs [1]. Recently a report by Laporte *et al.* has raised concern that nifedipine, a calcium-channel blocker (CCB), may be associated with an increased risk of aplastic anaemia [2]. As part of an ongoing case-control study of agranulocytosis and aplastic anaemia, Laporte *et al.* identified six cases of aplastic anaemia in persons exposed to nifedipine. In the study, which used hospitalized patients who did not have aplastic anaemia as a comparison group, the relative risk estimate (RR) of aplastic anaemia was reported to be 4.6 (95% CI 1.7,12.8) in nifedipine users relative to nonusers.

To examine further the relation between calcium channel blockers and aplastic anaemia we performed a population based study with a nested case-control analysis to evaluate the risk of newly diagnosed idiopathic aplastic anaemia in users of CCBs compared with that of other antihypertensive drugs. The study was based on information derived from the General Practice Research Database (GPRD) which is owned by the government of the United Kingdom.

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Methods

Since 1987, over 4 million residents of the United Kingdom have been enrolled by selected general practi-

tioners who use office computers provided by Value Added Medical Products and have agreed to provide data for research purposes to the GPRD. The general practitioners received 12 months of instruction on the standardized recording of medical information on computer, and they agreed to supply information without patient or practice identifiers to researchers on an ongoing basis. The information recorded on the computer includes the patient's characteristics (e.g. age, sex, smoking status, height, and weight), drugs prescribed, clinical diagnoses, notation of referrals to consultants and hospitals, and historical information. The general practitioners keep referral letters from consultants and hospital records in a manual file. These may be obtained through a unit located in the United Kingdom that has the ability to identify general practitioners who in turn can supply the records using an encrypted patient-identification number. All personal identifiers are removed from the patients' clinical records before they are sent. The general practitioners write prescriptions on the computer, and the details of each prescription, including the dose, any instructions, and the quantity, are automatically transcribed into the patients' computer records. A modification of the Oxford Medical Information System was used to classify medical diagnoses, and a coded dictionary based on the Prescription Pricing Authority's dictionary was used for prescriptions [3, 4]. The accuracy and comprehensiveness of the data recorded in the GPRD has been documented [3–6].

Study population

We conducted a follow-up study with a nested case-control analysis of idiopathic aplastic anaemia in a cohort of 322 448 subjects with treated hypertension. We identified all subjects who received at least one prescription for a calcium channel blocker, β-adrenoceptor blocker, angiotension-converting enzyme (ACE) inhibitor, α-adrenoceptor blocker, vasodilator, central sympatholytic or peripheral adrenergic antagonist for the period January 1, 1988 through September 30, 1997. Persons with a history of cancer, renal failure, liver failure, alcoholism or connective tissue disease prior to the first prescription for a study drug were excluded from the study.

Case ascertainment

We ascertained all subjects who had a first time computer-recorded diagnosis of aplastic anaemia or pancytopenia (ICD 284.9) after exposure to an antihypertensive drug. For each potential case we sent for all available clinical records, including hospital discharge summaries, referral letters and relevant laboratory reports. If a subject had died we requested that the general practitioner obtain the clinical records from the Family Health Services Association (FHSA) and all information relevant to the diagnosis of aplastic anaemia was sent to us for review.

The clinical records were reviewed without knowledge of exposure by a board-certified haematologist to determine case status. Subjects were excluded from further study if they had cancer, renal failure, liver failure, alcoholism, or a connective tissue disease that was not recorded in the computer record, or if the diagnosis of aplastic anaemia could not be confirmed. A subject was considered to have aplastic anaemia with a white blood cell count of $<3.5\times10^9$/l, a platelet count of $<50\times10^9$/l, and a haemoglobin of <100 g l^{-1} or haematocrit $<30\%$, together with a bone marrow evaluation consistent with a diagnosis of aplastic anaemia. The index date of the case from which drug exposure was derived was the date aplastic anaemia was first diagnosed.

Controls

Controls were selected without knowledge of exposure from among the base population of treated hypertensives who did not have aplastic anaemia. For each case we randomly selected six controls, matched for age (within 2 years), sex, general practice and calender time (same index date). The same exclusion criteria applied to cases were applied to controls.

Exposure

Antihypertensive drug exposure for case and control subjects was assessed from the computerized patient record. A subject was considered exposed to a study drug if they had received a study drug prescription within 90 days prior to the initial diagnosis of aplastic anaemia. In some subjects there were periods of follow-up in which they were not receiving antihypertensive drugs. Those who were not prescribed an antihypertensive drug in the 90 day window prior to diagnosis were considered nonexposed. Subjects who started their antihypertensive drug within 1 month before the diagnosis of aplastic anaemia were excluded.

All subjects were categorized into the following mutually exclusive categories: (1) nonexposed, (2) CCB exposure only, (3) β-adrenoceptor blocker exposure only, (4) ACE inhibitor exposure only, (5) 'other' (α-adenoceptor blocker, vasodilator, central sympatholytic, and peripheral adrenergic antagonist) antihypertensive drug use, (6) exposure to multiple drug categories with a CCB, and (7) exposure to multiple drug categories without a CCB. Also noted was the duration of exposure (number of prescriptions), and for users of CCBs, the specific preparation prescribed. In addition, we identified

exposure to other drugs that have been associated with aplastic anaemia.

Analysis

For the cohort analysis we calculated the risk of aplastic anaemia in two ways: first, as the number of cases in an exposure category divided by the number of users in that category and secondly, as the number of cases in a drug category divided by the total number of prescriptions received in the category. We also conducted a matched case-control analysis using conditional logistic regression models and obtained RR estimates (odds ratio) of aplastic anaemia with regard to antihypertensive drug use, using nonexposed as a reference group. Logistic regression was performed with SAS statistical software package (version 6.12, SAS Institute, Cary, North Carolina, USA).

Results

Cohort analysis

We identified 322 448 subjects who received a total of 10 148 828 prescriptions for an antihypertensive drug. The total person-time at risk for the cohort was 645 714 person-years. Among the subjects, 120 929 were exposed to CCBs (nifedipine = 73 338 subjects), 214 318 were exposed to β-adrenoceptor blockers, 85 140 used ACE inhibitors, 33 975 had received an 'other' antihypertensive drug and 2832 had received a combination preparation of CCB and β-adrenoceptor blocker. Most users (69%) were age 50 years or older with 26% over age 70 years.

From the computer records we identified 48 subjects with a computer-recorded diagnosis of aplastic anaemia or pancytopenia. Clinical records were obtained and reviewed for 38 (79%) of these potential cases. For the remaining subjects a determination of case status was based solely on the computer file. After review, 35 subjects were excluded from further study (Table 1). The remaining 13 were included as cases ($n=7$) or possible cases ($n=6$) of incident idiopathic aplastic anaemia. Cases were considered possible if the clinical diagnosis made by the consulting haematologist caring for the subject was aplastic anaemia but laboratory values were not available for our review. Among the 13 cases, there were seven cases in whom aplastic anaemia was attributed to a nonstudy drug (azathioprine, carbamazepine, methyldopa, amiodarone, sodium valproate, methotrexate, sulphasalazine) and one case in whom the illness was attributed to a viral infection. Furthermore, of the six possible cases, four had a nonstudy drug clinically implicated as the cause of aplastic anaemia. Seven of the cases died. Table 2 provides details of all the cases.

Table 1 Reasons for exclusions based on review of clinical and computer records*.

Reason	*Number of subjects*
Other diagnosis present**	27
Diagnosis not confirmed	5
Laboratory error/wrong entry	3
Total	35

*Five were based on the computer record alone.
**Includes myelodysplasia/myelofibrosis ($n=14$), liver disease ($n=4$), cancer ($n=2$), hypersplenism ($n=2$), monoclonal gammopathy ($n=1$), folate deficiency ($n=2$), renal disease ($n=1$), autoimmune disease ($n=1$).

Among the 13 cases, there was one case of aplastic anaemia in a subject currently exposed to diltiazem, a CCB, three cases among β-adrenoceptor blocker users, two cases among recipients of ACE inhibitors, two cases among users of 'other' antihypertensive drugs, and one case received multiple study drugs with a CCB – specifically nifedipine. There were four cases of aplastic anaemia among nonusers. The risk of aplastic anaemia per 100 000 users was 0.8 (95%CI 0.1, 4.7) in recipients of CCBs, 1.4 (95%CI 0.5, 4.1) among β-adrenoceptor blocker users, 2.3 (95%CI 0.6, 8.6) among users of ACE inhibitors and 5.9 (95%CI 1.6, 21.5) among recipients of 'other' antihypertensive drugs (Table 3). The risk per 1000 000 prescriptions was 0.3 (95%CI 0.1,1.9) in CCB users, 0.7 (95%CI 0.2, 2.1) in β-adrenoceptor blocker users, 1.0 (95%CI 0.3, 3.6) among users of ACE inhibitors and 2.5 (95%CI 0.7, 9.3) in recipients of 'other' study drugs (Table 3).

Case-control analysis

For the case-control analysis we identified 13 cases and 77 matched controls. Among the cases, one was below age 50 years, five were aged 50–69 years, and seven were age 70 years or older. The mean ages of the cases and controls were 69.6 and 68.8 years, respectively, and 47% of cases and controls were male.

Table 4 lists the odds ratio (OR) of aplastic anaemia according to antihypertensive drug exposure using nonexposed ($n=4$) as the reference group. The matched OR was 0.3 (95%CI 0.02, 3.3) for CCB users, 0.5 (95%CI 0.1, 2.5) for β-adrenoceptor blocker users, 0.7 (95%CI 0.1,5.6) among users of ACE inhibitors, 1.2 (95%CI 0.1, 11.8) for those exposed to 'other' antihypertensive drugs and 0.7 (95%CI 0.1,7.2) for those who received multiple study drugs with a CCB. There were no cases among subjects exposed to multiple antihypertensive drugs without a CCB. Stratification of the subjects into definite cases and possible cases did not substantially change the

Table 2 Characteristics of cases and possible cases with aplastic anaemia.

Patient	Age/Sex	Year of diagnosis	Case status	Exposure	Number of prescriptions prior to diagnosis	Comment
1	74 M	1989	Case	diltiazem	2	idiopathic, died
2	68 M	1994	Case	metoprolol	67	attributed to azathioprine which was discontinued, recovered
3	76 F	1992	Case	guanethidine	36	idiopathic, died
4	73 M	1993	Case	nonexposed	–	attributed to idiopathic or carbamazepine, died
5	76 M	1991	Case	captopril	4	attributed to parvovirus, chronic aplastic anaemia, died after 3 years
6	75 F	1990	Case	methyldopa, hydralazine unknown		attributed to methyldopa, all medications discontinued, died
7	68 M	1993	Case	atenolol	13	idiopathic, died due to myocardial infarction*
8	67 F	1996	possible	atenolol	100	hypoplastic anaemia, chronic*
9	69 F	1992	possible	nonexposed	–	attributed to amiodarone, also exposed to azathioprine, died*
10	53 F	1993	possible	nonexposed	–	hypoplastic, chronic, exposed to sulfasalazine
11	75 M	1993	possible	nifedipine, propranolol	28	chronic, diagnosis possibly myelodysplasia
12	80 F	1993	possible	captopril	6	attributed to sodium valproate, recovered*
13	51 F	1995	possible	nonexposed	–	attributed to methotrexate, also exposed to carbamazepine, recovered*

*Based on comments made on computer record.

RR estimate. Since the numbers were small and the confidence limits wide we analysed these groups together.

Discussion

Aplastic anaemia is a rare illness in the absence of treatment with anticancer drugs and other predisposing conditions. Laporte *et al*. recently reported on a positive association between nifedipine and the risk of developing aplastic anaemia [2]. Our study does not support these findings. In our large population-based study encompassing over 322 000 subjects, we found that exposure to CCBs compared with exposure to no antihypertensive drugs was not associated with idiopathic aplastic anaemia. In support of our results, a similar study by Kelly *et al*. which evaluated the risk of aplastic anaemia in relation to cardiovascular drugs reported a crude OR of 0.7 (95% CI 0.2, 2.2) for CCB users relative to nonuse [7]. Among the CCB cases ($n=3$), all were exposed to nifedipine yielding a crude OR of 1.7 (95% CI 0.5, 5.5).

The current study population included primarily elderly patients with treated hypertension. There is evidence that drug-induced blood disorders occur more frequently in the elderly [8]. The estimated annual risk for idiopathic aplastic anaemia of 2.0 per 100 000 person-years (13 cases/645 714 person-years at risk) was anticipated to be

Table 3 Incidence of aplastic anaemia according to current antihypertensive drug exposure.

Exposure*	Number of cases	Number of users	Incidence/100 000 users	95% CI	Number of cases	Number of prescriptions	Incidence/1000 000 prescription	95% CI
Nonexposed	4	–	–	–	4	–	–	–
CCBs	1	120 929	0.8	0.1, 4.7	1	3038 804	0.3	0.1, 1.9
β-adrenoceptor blockers	3	214 318	1.4	0.5, 4.1	3	4265 303	0.7	0.2, 2.1
ACE inhibitors	2	85 140	2.3	0.6, 8.6	2	2000 372	1.0	0.3, 3.6
Other**	2	33 975	5.9	1.6, 21.5	2	781 320	2.5	0.7, 9.3
Multiple study drugs with a CCB	1	–	–	–	1	–	–	
Multiple study drugs without a CCB	0	–	–	–	0	–	–	–

*Exposure categories are mutually exclusive.

**Includes α-adrenoceptor blockers, vasodilators, peripheral adrenergic antagonists, and central sympatholytics.

Table 4 Estimates of odds ratios for aplastic anaemia among cases and possible cases.

*Exposure**	*Cases (n = 13)*	*Controls (n = 77)*	*Odds ratio*	*95% CI*
Nonexposed**	4	15	1.0	Reference
CCBs	1	12	0.3	0.02, 3.3
β-adrenoceptor blockers	3	25	0.5	0.1, 2.5
ACE inhibitors	2	9	0.7	0.1, 5.6
Other	2	6	1.2	0.1, 11.8
Multiple study drugs with CCBs	1	6	0.7	0.1, 7.2
Multiple study drugs without CCBs	0	4	–	–

*Exposure categories are mutually exclusive.
**Reference group.

somewhat higher than the risk for a population which included all ages.

Despite the large size of the population included in the current study —322 000 subjects – and the person-time encompassed by the study estimated to be about 650 000 person-years, we did not anticipate finding many cases of idiopathic aplastic anaemia unless one of the antihypertensive study drugs was positively associated with this illness.

After careful review of all of the available evidence, we identified 13 cases which were considered to be definitely or possibly cases of idiopathic aplastic anaemia. For the cases where the evaluation was based on the computer record alone, there was sufficient information in the comments section to conclude that the diagnosis was at least possible. Importantly, among the 13 cases, there were seven in whom aplastic anaemia was attributed to a nonstudy drug. All of these drugs have been previously associated with drug-induced blood disorders [1, 8, 9].

The results provide no evidence that CCBs in general and nifedipine in particular are positively associated with the risk of aplastic anaemia. Given the small number of cases found and the wide confidence intervals we cannot rule out a modest effect, but our results are not compatible with a RR of 4.6 reported by Laporte *et al.* and are more consistent with the relative risk reported by Kelly *et al.* [7]

In summary, the current study provides evidence that CCBs in general and nifedipine in particular are not associated with an increased risk of aplastic anaemia.

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