Cohort study on calcium channel blockers, other cardiovascular agents, and the prevalence of depression

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Aims Some reports have suggested that calcium channel blockers may be associated with an increased incidence of depression or suicide. There is a paucity of evidence from large scale studies. The aim of this study was to assess rates of depression with calcium channel antagonists using data from prescription event monitoring studies.

Methods Observational studies on large cohorts of patients using lisinopril, enalapril (ACE inhibitors), nicardipine (type 2 calcium channel blocker) and diltiazem (type 3 calcium channel blocker) were conducted, using prescription-event monitoring. Rates of depression in the different drugs and rate ratios (95% CI) were computed.

Results The crude overall rates of depression during treatment were 1.89, 1.92 and 1.62 per 1000 patient months for the ACE inhibitors, diltiazem and nicardipine, respectively. Using the ACE inhibitors as the reference group, the rate ratios for depression were 1.07 (0.82–1.40) and 0.86 (0.69–1.08) for diltiazem and nicardipine, respectively.

Conclusions This study does not support the hypothesis that calcium channel blockers are associated with depression, when considering patients treated in general practice in the UK.

Keywords: adverse drug reaction, calcium channel blockers, depression

Introduction

Calcium channel blockers are used for the treatment of ischaemic heart disease and hypertension, and are generally well-tolerated. There have been some publications, however, suggesting that these drugs may be associated with an increased incidence of depressive disorders and suicide [1, 2], although another paper does not support this [3]. We report the rates of depression and number of suicides from prescription-event monitoring studies on calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors; we have computed rate ratios to compare depression in patients receiving the two types of drug.

Methods

Prescription-event monitoring (PEM) involves gathering information on symptoms or diagnoses (events) occurring to patients after prescription of a study drug by general practitioners. Exposure and event (outcome) data on approximately the first 10,000 patients on a newly marketed drug are studied. The technique of PEM has been described in full elsewhere [4]. It is essentially a hypothesis-generating technique. The following drugs, studied by this method, were included in this study: nicardipine (type 2 calcium channel blocker), diltiazem (type 3 calcium channel blocker), lisinopril and enalapril (angiotensin converting enzyme inhibitors). The studies were conducted between September 1984 and March 1989. These drugs were chosen because they were studied by PEM at approximately the same time, were indicated for cardiovascular problems, and had equivalent response rates to the PEM outcome questionnaire. They are therefore the most comparable drugs in the PEM database. For comparison, we report crude event rates also for 38 other long-term use drugs (ranging from antiepileptics to proton pump inhibitors), studied by PEM. The term depression was chosen for the main outcome, since there were sufficient events to allow meaningful statistical comparisons. This term includes any events written by the GP as ‘depression’, but also includes other events coded to ‘depression’, according to the system-organ dictionary developed for PEM. Examples of such events are neurotic depression, manic depression, postnatal depression and depressed mood. Thus the definition of ‘depression’, as used in this study, is wide-reaching. Suicides and suicide attempts in each drug

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Received 13 January 1999, accepted 26 March 1999.

cohort were too low to allow valid statistical analysis, but the numbers are reported. Outcome events occurring during treatment in the first 6 months were used as the numerator for the rates and rate ratios. Crude event rates for depression per 1000 patient months of treatment during the first month and during months 2–6, and the difference between the two (with 99% CI) were calculated from the PEM studies. Crude and adjusted rate ratios for the whole 6 month period were calculated: potential confounders were identified as age (categorized in quartiles), sex, season and indication (four categories: ischaemic heart disease, hypertension, cardiac failure and others). The results were adjusted by Poisson regression models, using the statistical package Stata 5 (Statacorp, Texas).

Results
The results from the PEM studies (see Table 1) show that the cohort sizes are large—in excess of 10,000 patients for each drug—and that the difference in rates of depression for month 1 and months 2–6 (ID1–ID2) are not significantly different from 0 for any of the drugs. The number of suicides/suicide attempts is very low.

ID1 of depression for 38 other long-term use drugs on the PEM database was 2.9 per 1000 patient months, and ID2 was 1.9 per 1000 patient months. These rates are very similar to those shown in Table 1 for the selected drugs.

Table 1 shows the summary characteristics of the cohorts, as used for the calculation of adjusted rate ratios. For the purposes of the calculation of the rate ratios, the ACE inhibitor drugs have been combined, since there was no significant difference in the overall rates of depression between the two individual drugs. Although the age distribution of the cohorts is very similar between the different drugs, there were significant differences between the sex distribution (P<0.001), the predominant indication (P<0.001), and the season of start of therapy (P<0.001).

The results in Table 3 show that depression is reported rather uncommonly, and that the rate shows little difference between the drug groups. Thus the crude rate ratios for depression in the calcium channel blockers are very close to, or equal to, one when compared to ACE inhibitors. Adjustment for potential confounders makes very little difference to the rate ratios.

Discussion
In PEM studies, one type of ‘signal’ of a potential adverse drug reaction (ADR) is represented by a difference between ID1 and ID2, where P<0.01. This is because typical type A ADRs tend to occur in the first month of treatment, and the incidence then returns to a plateau level (indicative of the background rate) during later months of treatment. The results from the PEM studies of these drugs did not generate such a ‘signal’ that depression was an ADR. Although this may indicate that there was truly no ADR, there are other possible explanations: it could be due to the long latency of development of depression, or selective under-recording of depression, and it does not take into account any confounding factors. Therefore it was necessary to do a comparative study, in which adjusted rates of depression for the whole period of treatment were compared between drugs, and this comprises a comparatively simple way of testing the hypothesis generated by other studies. This comparative study has not shown any evidence of an association between the diagnosis of depression and use of calcium channel blockers.

It is possible that there is under-reporting of depression in our cohorts, either through nonresponse to the questionnaires or due to incomplete records on the returned forms. Paykel [5] quotes a prevalence of 5% for major depression and a further 5% for minor depression in consulters in general practice. However, it is widely recognized that the diagnosis of depression is frequently missed in general practice, and even if it is recognized, it may not be recorded in the notes. Morbidity data from

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Table 2

Summary statistics of cohorts used for calculation of adjusted rate ratios.

<table>
<thead>
<tr>
<th></th>
<th>ACE inhibitors</th>
<th>Diltiazem</th>
<th>Nicardipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (s.d.) age of cohort</td>
<td>61.1 (12.1)</td>
<td>62.3 (10.9)</td>
<td>62.9 (11.3)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>45.8</td>
<td>60.0</td>
<td>48.6</td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>0.4</td>
<td>57.3</td>
<td>31.2</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>3.7</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>54.9</td>
<td>1.5</td>
<td>56.0</td>
</tr>
<tr>
<td>Others (%)</td>
<td>41.0</td>
<td>40.9</td>
<td>12.2</td>
</tr>
<tr>
<td>Season at start of therapy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>20.9</td>
<td>19.8</td>
<td>30.3</td>
</tr>
<tr>
<td>Spring</td>
<td>13.6</td>
<td>28.4</td>
<td>32.7</td>
</tr>
<tr>
<td>Summer</td>
<td>28.6</td>
<td>33.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Autumn</td>
<td>36.8</td>
<td>18.9</td>
<td>24.9</td>
</tr>
<tr>
<td>Median (interquartile range), days of follow-up</td>
<td>179 (117–388)</td>
<td>406 (87–451)</td>
<td>383 (132–417)</td>
</tr>
<tr>
<td>% with depression</td>
<td>1.44</td>
<td>1.61</td>
<td>1.91</td>
</tr>
</tbody>
</table>

Table 3

Rates and rate ratios (ACE inhibitors as comparison group) for depression.

<table>
<thead>
<tr>
<th></th>
<th>ACE inhibitors</th>
<th>Diltiazem</th>
<th>Nicardipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude rate of depression*</td>
<td>1.89</td>
<td>1.92</td>
<td>1.62</td>
</tr>
<tr>
<td>Crude rate ratio of depression</td>
<td>1</td>
<td>1.00</td>
<td>0.84</td>
</tr>
<tr>
<td>Adjusted rate ratio of depression (95% CI)</td>
<td>1</td>
<td>1.07 (0.82–1.40)</td>
<td>0.86 (0.69–1.08)</td>
</tr>
</tbody>
</table>

*Per 1000 patient months of treatment.

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the General Practice Research Database [6] shows that the prevalence of recorded depression in a single year varies between 1.2% and 1.7% of the population of 50–70 year olds, rates which agree with the data from the present study, where most of the patients were of this age. Thus although it is likely that depression is under-recorded in these data, this is not unexpected, and is no worse than in another comparable GP database. Furthermore, there is no reason to suppose that this is differential between the study drugs, and thus the rate ratios should give a true measure of effect. Equally, although the response rate to the original mailing was about 60% in all the cohorts, and we have no estimate of the prevalence of the nonresponders, it is unlikely that this would introduce a bias into the calculation of rate ratios. The rates of depression in the 28 other long-term use drugs on the PEM database do not suggest that there is any particular reporting bias in the selected, cardiovascular, drugs. The calendar periods during which data were collected varied between the drugs under study (between 1984 and 1989), but there is considerable overlap between the calcium channel blockers and the ACE inhibitors. This study is unable to differentiate between incident and chronic cases of depression, but this should not matter, since there is no particular reason for one type of drug to be given preferentially to patients with a known diagnosis of depression.

The putative association between calcium channel blockers and depression and suicide is contentious. Lindberg [1] suggested that suicide rates are related to use of calcium channel blockers. This was based on an ecological study, which can only be considered hypothesis-generating, and on the results of a cohort study with wide confidence limits for the main outcome measure (relative risk for suicide of 5.4, 95% CI 1.4–20.5, among 50–70 year olds, rates which agree with the data from the present study, where most of the patients were of this age. Thus although it is likely that depression is under-recorded in these data, this is not unexpected, and is no worse than in another comparable GP database. Furthermore, there is no reason to suppose that this is differential between the study drugs, and thus the rate ratios should give a true measure of effect. Equally, although the response rate to the original mailing was about 60% in all the cohorts, and we have no estimate of the prevalence of the nonresponders, it is unlikely that this would introduce a bias into the calculation of rate ratios. The rates of depression in the 28 other long-term use drugs on the PEM database do not suggest that there is any particular reporting bias in the selected, cardiovascular, drugs. The calendar periods during which data were collected varied between the drugs under study (between 1984 and 1989), but there is considerable overlap between the calcium channel blockers and the ACE inhibitors. This study is unable to differentiate between incident and chronic cases of depression, but this should not matter, since there is no particular reason for one type of drug to be given preferentially to patients with a known diagnosis of depression.

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Cohort study on calcium channel blockers

We would like to record our keen appreciation of the co-operation of general practitioners in England in the conduct of PEM studies. The calculated measures of effect were not large, and there are a number of other possible explanations for the results other than cause and effect. Patten [3] carried out a cross-sectional study of drug exposure in medical in-patients with, and without, depressive symptoms and could find no association with calcium channel blockers. However, rather small numbers of patients were involved (227), and they were nonrandomly selected volunteers, which limits the generalizability of the findings. Gerstman [7] reported the results of a historical cohort study in a large number of patients in a U.S. health maintenance organization. Again, this study was primarily looking for any association between $\beta$-adrenoceptor blocker drugs and depression, but did identify 742 users of calcium channel blockers. These were followed up for 6 months. The unadjusted rates of major and minor depression diagnoses combined were similar in the $\beta$-adrenoceptor blocker group (20.2 per 1000 person years), ACE inhibitor group (26.9 per 1000 patient years) and the calcium channel blocker group (16.9 per 1000 patient years). Although these results have obvious limitations since they are not adjusted for confounders in any way, they do not suggest any difference between the drug groups. Other publications on this subject have been case reports or case series [6, 9], which need confirmation in hypothesis-testing studies.

Overall therefore there is a paucity of good scientific evidence on this matter. The results from the present epidemiological study on large, general practice, patient cohorts do not offer any support to the hypothesis that calcium channel blockers are associated with depression. We would like to record our keen appreciation of the cooperation of general practitioners in England in the conduct of PEM studies. We would also like to thank the Prescription Pricing Authority for their important contribution. Mrs Jan Phillips gave untiring secretarial support. The DSRU is a charity supported by voluntary contributions from many pharmaceutical companies. This study was not funded specifically by any individual company. There is no conflict of interest.

References