Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database

Nicholas Moore,[1,2] Carmen Kreft-Jais,[3] Françoise Haramburu,[2] Catherine Noblet,[1] Michel Andrejak,[4] Michel Ollagnier[5] & Bernard Bégaud[2]

French Pharmacovigilance System, Regional Pharmacovigilance Centres at [1]Rouen, [2]Bordeaux, [3]Broussais, [4]Amiens, [5]French Association of Regional Pharmacovigilance Centres, With the assistance of all 31 Regional Centres of the French Pharmacovigilance System, and of the Pharmacovigilance unit, French Medicines Agency, Paris, France

Aims To test the existence of an association between reports of hypoglycaemia and angiotensin converting enzyme inhibitors, in a spontaneous reports database.

Methods The French Pharmacovigilance database was examined for an association between adverse drug reaction reports mentioning hypoglycaemia, and angiotensin converting enzyme inhibitors (ACEI) using the case/non-case methodology, with reports of hypoglycaemia as cases and all other reports as comparators. The association between ACEI or other chosen drugs and hypoglycaemia was also tested in the subgroups of patients taking or not antidiabetic agents (ADA).

Results 428 of 93338 reports mentioned hypoglycaemia (202/2227 with ADA (OR 40, 95% CI 33–48)). 46/5717 reports mentioned ACEI (OR 1.8 (1.25–2.54)). Other study drugs associated with hypoglycaemia were cibenzoline (OR 80 (57–112)), disopyramide (OR 32 (22–46)), nifedipine (OR 2.16 (1.32–3.51)), diltiazem (OR 1.76 (1.01–3.06)) nitrates (nitroglycerin, molsidomine) (OR 1.91 (1.16–3.16)) and frusemide (OR 1.89 (1.31–1.76)), but not nicardipine, amlodipine, felodipine or nitrendipine, diazepam, atenolol or combination thiazide diuretics. However, ACEI and other drugs were associated with ADA, so that in the subgroups of patients taking or not ADA, the association of ACEI with hypoglycaemia disappeared (OR 0.9 (0.5–1.4) and 1.2 (0.7–2.2), respectively). The same was found for other drugs except cibenzoline.

Conclusion The association between reporting of hypoglycaemia and ACE inhibitors was related to concomitant use of antidiabetic agents. This was true also for other drugs used in arterial disease or renal failure, such as calcium channel blockers, nitrates, and frusemide.

Keywords: spontaneous reporting databases, case-non-case methodology, hypoglycaemia, ACE inhibitors, diabetics

Introduction

There have been sporadic reports of hypoglycaemia associated with the use of angiotensin converting enzyme inhibitors (ACEI) [1–5]. They have usually but not always occurred in diabetic patients treated with antidiabetic agents. Formal clinical trials have not, however, consistently shown any clear interactions between ACEI and antidiabetic agents or insulin secretion [6–8]. A nested case-control study in the Dutch Pharmo system has found a clear association between ACEI and hypoglycaemia in users of insulin or oral hypoglycaemic agents (odds ratio 2.8 (1.4–5.7)). The association seemed stronger, though not significantly so, in users of oral hypoglycaemic agents compared with insulin [9].

An analysis of reports of hypoglycaemia in the French Pharmacovigilance database [10] found that ACEI were the most frequent non-hypoglycaemic drug mentioned in antidiabetic agent-associated reports of hypoglycaemia, closely followed by other drugs such as diuretics [11].

On the same dataset, using case/non-case methodology, we attempted to test the association of ACEI and hypoglycaemia. The main hypothesis was that there could be excess reporting of hypoglycaemia associated with ACEI in all subjects. A secondary objective was to explore and compare this association in users and non-users of antidiabetic agents (presumed to be diabetics and non-diabetics).

Methods

The study used data from the French Pharmacovigilance database of case reports. This database includes all adverse drug reactions reported to the French Regional Pharmacovigilance Centres since 1985 [10] by health professionals, but not those reported to manufacturers. All reactions are coded according to the WHOART dictionary.

Correspondence: Dr Nicholas Moore, Department of Clinical Pharmacology, University of Bordeaux II, CHU Pellegrin Zône Nord Bat 1A, 33076 Bordeaux, France.

Reports are reviewed by the medically qualified personnel in the Regional Centres before being put into the database. All available data are considered to arrive to a diagnosis and coding which is as accurate as possible.

The case/non-case method used is as follows: cases and non-cases are both identified from the spontaneous ADR reporting database. Cases are reports of the reaction of interest (ie hypoglycaemia). Non-cases (or comparators) are all reports of reactions other than that being studied. Exposure is considered as the presence in a report of the drug of interest, whether or not it is suspected of causing the reaction. The odds ratio (OR) is the ratio of the odds of the association of reports of the reaction of interest with the drug(s) of interest in cases and in non-cases. It is computed as ad/bc, where a is the number of exposed cases, b the number of unexposed cases, c the number of exposed controls, and d the number of unexposed controls. The 95% confidence interval (95% CI) is computed according to the usual methods (the limits are $OR \exp(\pm 1.96\sqrt{1/a+1/b+1/c+1/d})$) [12]. The null hypothesis is that the exposure rate in cases is not different from that in non-cases, in which case the 95% confidence interval of the odds ratio includes 1. An odds ratio whose confidence interval does not include 1 is considered significantly different from 1. If the odds ratio is greater than 1, as defined above, it can be interpreted as indicating an association between the drug(s) and reporting of the reaction(s) of interest. This method can be thought akin to a variant of the database nested case-control method [12, 13], or to the study of proportional mortality ratios used in cancer research.

Reports of hypoglycaemia were taken as cases, and all other reports in the database as non-cases. Since all reports in the database are reviewed by qualified personnel prior to entry into the database, it was not judged necessary to review again individual case reports for misdiagnosis or misclassification. There was no indication in the data as to seriousness of the reaction (i.e. hospitalisation) nor severity of hypoglycaemia.

The cases and non-cases were examined for the presence of selected drug classes, and some associations. The classes and drugs studied were the following

— antidiabetic agents (ADA) i.e. sulphonylureas, insulin, metformin;

— captopril, enalapril and other angiotensin converting enzyme inhibitors (ACEI);

— other drugs used as negative and positive controls to test the ability of the methods to identify or recognize the association: diazepam as a control drug not associated with hypoglycaemia, and cibenzoline and disopyramide as control drugs known to be causally associated with hypoglycaemia [14–19];

— drugs used in the same indications as ACEI: calcium antagonists, diuretics, atenolol, or that could be markers of specific associated diseases, especially diabetic microangiopathy such as nitrates, were also studied, to test for confounding by indication.

The analysis was first performed in the whole database, then separately in diabetic and non-diabetic patients, identified as users and non-users of anti-diabetic agents.

Results

Table 1 shows the rates of hypoglycaemia reports with antidiabetic agents for the complete database, Table 2 with selected non-antidiabetic agents, Table 3 the association between these and ADA, and Tables 4a and 4b the associations with hypoglycaemia respectively in diabetic and non-diabetic patients.

There were 428 reports of hypoglycaemia, representing 0.5% of 93338 reports to the Regional Pharmacovigilance Centres, in the French Pharmacovigilance database at the time of the analysis, covering a 10-year period from 1985 to 1994.

a) Antidiabetic agents

Of the 428 reports mentioning hypoglycaemia, 202 occurred in patients taking antidiabetic agents (ADA), representing 9%

Table 1 Association of antidiabetic agents (ADA) with hypoglycaemia in the French Pharmacovigilance database: number of reports including the drug(s).

	All reports	*Hypoglycaemia*	*%*	*OR*	*95% CI*	
All reports	93338	428	0.5			
Insulin	397	32	8.1	20.5	14.1	29.8
Metformin	767	40	5.2	13.1	9.4	18.3
Gliclazide	680	76	11.2	33.0	25.4	42.8
Glibenclamide	577	71	12.3	36.3	27.8	47.5
Chlorpropamide	40	4	10.0	24.3	8.6	68.7
Tolbutamide	9	1	11.1	27.2	3.4	217.9
Glibornuride	22	1	4.6	10.4	1.4	77.2
Carbutamide	89	4	4.5	10.3	3.8	28.2
Glipizide	97	11	11.3	28.5	15.1	53.7
Any sulphonylurea	1480	167	11.3	44.6	36.5	54.6
Any ADA	2227	202	9.1	40.1	33.0	48.7

Legend: %: percent ratio of hypoglycaemia reports to all cases; OR: odds ratio of association of selected drug with hypoglycaemia, compared with all reports; 95% CI: lower and upper limits of 95% confidence interval for OR; the odds ratio is computed by the ratio of the rates of reporting hypoglycaemia rather than another reaction with or without the drug of interest (e.g., for insulin, (32/365)/(396/92545), i.e., (hypoglycaemia with insulin/other reports with insulin)/(hypoglycaemia without insulin/other reports without insulin).

Table 2 Association of individual non-antidiabetic drugs with hypoglycaemia in the French Pharmacovigilance database (all reports).

	All reports	*Hypoglycaemia*	*%*	*OR*	*95% CI*	
All reports	93338	428	0.5			
Any ACEI	5717	46	0.8	1.9	1.4	2.5
Captopril	2588	17	0.7	1.4	0.9	2.4
Enalapril	1763	17	1.0	2.2	1.3	3.5
Lisinopril	500	3	0.6	1.3	0.4	4.1
Perindopril	324	2	0.6	1.3	0.3	5.4
Ramipril	249	4	1.6	3.6	1.3	9.6
Quinapril	149	1	0.7	1.5	0.2	10.5
Benazepril	133	1	0.7	1.6	0.2	11.8
Cilazapril	11	0	–	–	–	–
Diazepam	567	2	0.4	0.8	0.2	3.1
Disopyramide	309	37	12.0	32.2	22.5	46.1
Cibenzoline	206	50	24.6	78.7	56.3	109.9
Atenolol	701	3	0.4	0.9	0.3	2.9
Diuretics	1829	7	0.4	0.8	0.4	1.8
Frusemide	3846	32	0.8	1.9	1.3	2.7
Nifedipine	1765	17	1.0	2.2	1.3	3.5
Nicardipine	1232	8	0.7	1.4	0.7	2.9
Nitrendipine	294	1	0.3	0.7	0.1	5.3
Diltiazem	1642	13	0.8	1.8	1.01	3.1
Verapamil	421	4	1.0	2.1	0.8	5.6
Nitrates	1863	16	0.9	1.9	1.2	3.2

Legend: %: percent ratio of hypoglycaemia reports to all cases; OR: odds ratio of association of selected drug with hypoglycaemia, compared to all reports. The odds ratio is computed by the ratio of the rates of reporting hypoglycaemia rather than another reaction with or without the drug of interest (e.g., for ACEI, (46/5671)/(382/87239), i.e., (hypoglycaemia with ACEI/other reports with ACEI)/(hypoglycaemia without ACEI/other reports without ACEI); 95% CI: lower and upper limits of 95% confidence interval for OR; ACEI: Angiotensin converting enzyme inhibitor; diuretics: combined amiloride-thiazide or combined spironolactone-thiazide; nitrates: nitroglycerin or molsidomine.

Table 3 Concomitant presence of antidiabetic agents (ADA) and other drugs in the French Pharmacovigilance database.

	All reports	*Associated with ADA*	*%*	*OR*	*95% CI*	
All reports	93338	2227	2.4			
ACEI	4322	272	6.3	3.0	2.6	3.4
Enalapril	1763	90	5.1	2.3	1.8	2.8
Captopril	2588	110	4.3	1.9	1.5	2.3
Diazepam	567	7	1.2	0.5	0.2	1.1
Cibenzoline	203	9	4.4	1.9	0.96	3.7
Atenolol	724	38	5.2	2.3	1.6	3.2
Diuretics	1847	111	6.0	2.7	2.2	3.3
Frusemide	3846	242	6.3	2.9	2.6	3.4
DHP	3276	214	6.5	3.1	2.6	3.5
Verapamil	421	24	5.7	2.5	1.7	3.8
Diltiazem	1642	103	6.3	2.8	2.3	3.5
Nitrates	1863	105	5.6	2.5	2.1	3.1

Legend: %: percent ratio of reports associated with ADA; OR: odds ratio of association of ADA with selected drug; 95% CI: lower and upper limits of 95% confidence interval for OR; ACEI: converting enzyme inhibitors (enalapril or captopril); diuretics: thiazide combination diuretics; DHP: dihydropyridine (nifedipine, nicardipine, nitrendipine, nimodipine); nitrates: nitroglycerin or molsidomine.

of the 2227 reports mentioning ADA (OR of the association of hypoglycaemia with ADA 40 (95% CI 33–48)). Reporting rates for individual ADAs are given in Table 1.

b) Angiotensin converting inhibitors (ACEI)

There were 46 reports mentioning hypoglycaemia, out of 5717 reports mentioning ACEI, irrespective of ADA status (OR 1.9 (1.4–2.5)), of which 34 concerned either captopril or enalapril (out of 4322 reports mentioning either, OR 1.8 (1.3–2.5)). Reporting rates for hypoglycaemia with other ACEI are given in Table 2.

Of the 4322 reports mentioning captopril or enalapril, 272 were in ADA users (Table 3). The association of ADA and ACEI was higher than expected from the reporting frequency for either (OR of the association 3.0 (2.6–3.4)

Table 4a Association of non-antidiabetic drugs with hypoglycaemia in the French National Pharmacovigilance database, in reports not including antidiabetic agents (non-diabetics).

	All reports	*Hypoglycaemia*	*%*	*OR*	*95% CI*	
All reports	91111	226	0.3			
ACEI	4050	12	0.3	1.2	0.7	2.2
DHP	3062	12	0.4	1.6	0.9	2.9
Diltiazem	1539	6	0.4	1.6	0.7	3.6
Verapamil	397	2	0.5	2.0	0.5	8.3
Nitrates	1758	7	0.4	1.6	0.8	3.5
Frusemide	3604	17	0.5	2.0	1.2	3.2
Cibenzoline	197	47	23.9	158.8	110.9	227.4

Table 4b Association of non-antidiabetic drugs with hypoglycaemia in the French National Pharmacovigilance database, in reports including antidiabetic agents (diabetics).

	All reports	*Hypoglycaemia*	*%*	*OR*	*95% CI*	
All reports	2227	202	9.1			
ACEI	272	22	8.1	0.9	0.5	1.4
DHP	214	14	6.5	0.7	0.4	1.2
Diltiazem	103	7	6.8	0.7	0.3	1.6
Verapamil	24	2	8.3	0.9	0.2	3.9
Nitrates	105	9	8.6	0.9	0.5	1.9
Frusemide	242	15	6.2	0.6	0.4	1.1
Cibenzoline	9	3	33.3	5.1	1.3	20.4

Legend: %: percent ratio of hypoglycaemia reports; OR: odds ratio of association of selected drug with hypoglycaemia (see Table 2); 95% CI: lower and upper limits of 95% confidence interval for OR; ACEI: angiotensin converting enzyme inhibitor (enalapril or captopril); DHP: dihydropyridines (nifedipine, nicardipine, nitrendipine, or nimodipine); nitrates: nitroglycerin or molsidomine.

(Table 3). When analysed separately in ADA users and non-users (diabetics or non-diabetics), we found no association between the presence of hypoglycaemia and ACEI: OR in non-diabetics and diabetics were respectively 1.2 (0.7–2.2) and 0.9 (0.5–1.4) (Tables 4a and 4b), so that in fact the association of ACEI with hypoglycaemia was related to their association with ADA. In ADA users, concomitant presence of ACEI did not increase the risk of reporting hypoglycaemia.

c) Negative and positive controls for hypoglycaemia

Diazepam was chosen as a negative control, not being usually associated with hypoglycaemia, or with diabetes. Of the 567 reports mentioning diazepam, two were of hypoglycaemia (OR 0.8 (0.2–3.1)) and seven were associated with ADA (OR 0.5 (0.2–1.1)).

Cibenzoline and disopyramide, two class 1a antiarrhythmics known to cause hypoglycaemia, were chosen as positive controls. For disopyramide, 37 of 309 reports were of hypoglycaemia (OR 32 (23–46)). For cibenzoline, 50 of 206 reports were of hypoglycaemia (OR 79 (56–110)). Cibenzoline use was not associated with ADA (9 reports, OR 1.9 (0.96–3.7), and the association with hypoglycaemia was found in non-diabetics (47 of 197 reports, OR 159 (111–227)), and in diabetics (3 of 9 reports, OR 5 (1.3–20)). Cibenzoline is associated with hypoglycaemia in non-diabetic patients, and increases the risk of reporting hypoglycaemia in ADA users.

d) Controls for indication

Other drugs with the same indications as ACEI (hypertension and heart failure) were also tested for association with hypoglycaemia in diabetics and non-diabetics: these include atenolol, diuretics, and calcium antagonists.

Atenolol was not associated with hypoglycaemia in the whole database (3 of 701 reports, OR 0.93 (0.3–2.9)).

Combination diuretics were not associated with hypoglycaemia in the whole database (7 of 1847 reports, 0R 0.8 (0.4–1.8)), but frusemide was (32 of 3846 reports, OR 1.9 (1.3–2.7)). Frusemide was also associated with ADA (242 reports, OR 2.9 (2.6–3.4). However, though there was no association with hypoglycaemia in diabetics (15 of 242 reports, OR 0.6 (0.4–1.1)), there was still excess reporting of hypoglycaemia in non-diabetics (17 of 3604 reports, OR 2.0 (1.2–3.2)).

Calcium antagonists, especially those more often prescribed in ischaemic heart disease, were also associated with hypoglycaemia in the whole database: nifedipine (17 of 1765 reports, OR 2.2 (1.3–2.7)), diltiazem (13 of 1642 reports, OR 1.8 (1.01–3.1)), verapamil (4 of 421 reports, OR 2.09 (0.8- 5.6)). These drugs were associated with ADA (Table 3), so that the association with hypoglycaemia was no longer apparent in diabetics or non-diabetics when studied separately (Tables 4a and 4b).

The same was true with nitrates, whose association with hypoglycaemia (16 of 1863 reports, OR 1.9 (1.2–3.2) was also related to association with ADA: hypoglycaemia represented in non-diabetics 7 of 1758 reports, OR 1.6 (0.8–3.5), in diabetics 9 of 105 reports, OR 0.9 (0.5–1.9).

To summarize, for all drugs except cibenzoline (and perhaps frusemide), the association with hypoglycaemia in all reports in the database was related to use of antidiabetic agents. In patients not taking antidiabetic agents (non-diabetics), we did not find any association of hypoglycaemia with ACEI.

Discussion

This study did not confirm previous findings of an association of angiotensin converting inhibitors with hypoglycaemia, either in diabetics or in non-diabetics. Our study used a case/non-case approach within a spontaneous reporting database. It has the advantage that all the information is already in the database, and is readily available for analysis. On the other hand, it compounds some of the difficulties of case-control methods with those of spontaneous reporting.

The case/non-case method compares the relative reporting of a reaction (case) compared with all other reactions reported and looks for associations with specific drugs, whether or not thought causal to the reaction. The association between the drug of interest and the reaction is measured by an odds ratio, in essence a comparison of the adverse reaction profiles or reporting ratios of the drug of interest with those of all other drugs. The odds ratio is increased when, relative to other drugs, the drug of interest is more often associated with the reports of the reaction.

Associations may be present because the reaction is more frequent, or because is more often reported. The ratio may also be increased because other reactions are less frequent or less reported. It may be decreased by under-reporting of the reaction of interest. This could be the case for a new drug in an established class, where class effects would tend to be less reported than for the first drugs in the class. However, if the drug is marketed with the claim that it is safer or gives fewer reactions than older drugs, the occurence of a reaction may give rise to increased reporting, especially if there is a chanelling effect to the new drug for patients who have had problems with previous drugs, and may be more at risk of having problems with the new drug.

The association between a drug and a reaction may also be decreased artificially if another reaction, specific to the drug, is much reported, thereby diluting the association by increasing the presence of the drug in the non-case reports.

Many factors influence both the reporting and the content of the report [13, 20]. Regular under-reporting (where all drugs reactions in a class are similarly under-reported) would not produce a systematic bias, but uneven under-reporting may be a significant problem. The two of the more commonly alleged factors leading to under-reporting are non-recognition of the reaction as being drug-related, and knowledge (labelling) of the reaction: a well-known reaction may not be reported. Low reporting of a known reaction can also be related to true prevention of the reaction. High reporting of a reaction can be related to high visibility of the reaction (e.g., a new reaction to a new drug, a media effect), or to increased frequency of the reaction. This is especially important for the comparison of drugs within the same therapeutic class, where the age of the drug, its indications, and its overall perception by the prescriber may exert great influence on reporting patterns. For these reasons, it is important when using this method, to test comparator drugs, known to be associated or not with the reaction (in our example, cibenzoline and diazepam), and to try to compare drugs within a class or with other drugs with the same indications (e.g., in our case, calcium channel blockers, β-adrenoceptor blockers, diuretics). It is also important to try to compare drugs with the same market age: most of the ACE inhibitors except captopril and enalapril were marketed within a comparable time-frame, and within the complete time-frame of the database.

No matching of cases and comparators was made, and there was no reascertainment of case data. Data ascertainment and quality control is made at data entry by the personnel of the regional centre who receive and input the data [10] following Good Pharmacovigilance Practices [21]. The absence of matching is an *a priori* choice common in case-cohort studies. In the present analysis, we used as comparators the rest of the database, but subgroup analysis in diabetic patients does effect some matching.

Our results show that if ACE inhibitors are associated with reports of hypoglycaemia, it is through concomitant use of ADA. ACEI do not seem to increase the risk of reporting hypoglycaemia in ADA users (diabetics). The same association was found with certain calcium channel blockers, but not with atenolol, one of the more commonly prescribed β-adrenoceptor blockers, or with the two most widely used thiazide diuretics, though it was found for frusemide. For frusemide, an unexplained association with reports of hypoglycaemia remained in non-diabetic patients. Hypoglycaemia is not a known ADR for frusemide, which tends to induce hyperglycaemia. This may be a spurious finding related to chance and the number of tests done.

The association of the drugs above with ADA is not surprising, diabetes being a major risk factor for arterial disease, including microangiopathy, and renal disease, all of which are indications for these cardiovascular agents. However, their association with ADA does not increase the risk of reporting hypoglycaemia relative to other reactions, compared to the use of ADA alone.

Our results differ from those of Herings and colleagues [9], in that we did not find an increased risk of reporting hypoglycaemia in patients taking ACEI and ADA compared with ADA alone. However, these authors studied the risk of hospitalization in diabetic users of ACEI whereas we studied the risk of reporting hypoglycaemia relative to other adverse reactions, irrespective of the severity of hypoglycaemia, or of hospitalization. Two hypotheses can be advanced to explain the discrepancy between the present results and those of Herings [9]. It may be that ACEI increase the risk of all reactions when associated with ADA, thereby not altering the hypoglycaemia/not hypoglycaemia ratio, or ACEI increase the severity of hypoglycaemia, resulting in more frequent hospital admissions (or even with similar severity hypoglycaemia, unexpectedness of hypoglycaemia with ACEI may lead to exploratory hospitalisation). In both cases, there would be an increased identification of hypoglycaemia in a study only of hospitalized hypoglycaemia. This study does not contradict Herings' work, nor does it disprove the individual case reports of ACE inhibitor-associated hypoglycaemia: there are enough to suggest that hypoglycaemia may indeed be a side-effect of ACE inhibitors. Unfortunately, we do not have any indication of hospitalization in our database, so we cannot directly compare our data with those of Herings and colleagues.

Conclusions

We did not find increased risk of reporting hypoglycaemia with ACE inhibitors in diabetic or in non-diabetic patients. We found increased association of ACE inhibitors and of other drugs used in the treatment or arterial disease or hypertension with antidiabetic agents. We confirmed the reporting of hypoglycaemia associated with cibenzoline, which is increased by concomitant use of ADA.

The case/non-case method in pharmacovigilance databases uses existing data that are readily available and exist in most or all industrial countries. The data are centred on the field of interest, drug safety. This is not the case for most other existing databases, which have usually been established for purposes such as health insurance. This use of pharmacovigilance databases is rather unusual, though examples have already been described [22]. The advantages and limits of the method should be further explored and tested for other drug-reaction associations. This method could represent an useful adjunct to other epidemiological tools, especially when one considers the small number of large population databases.

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