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A signal of increased risk of hypoglycaemia with angiotensin receptor blockers caused by confounding

Fleur Grégoire,[1] Antoine Pariente,[1,2,3] Annie Fourrier-Reglat,[1,2,3] Françoise Haramburu,[1,2] Bernard Bégaud[1,2,3] & Nicholas Moore[1,2,3]

[1]CHU de Bordeaux, [2]INSERM, U657 and [3]Universite Victor Segalen, Department of Pharmacology, Bordeaux, France

Correspondence
Dr Antoine Pariente, MD, INSERM U657, Department of Pharmacology, BP 36, Université Bordeaux 2, F33076 Bordeaux, France.
Tel: +33 5 57571560
Fax: +33 5 57574671
E-mail: antoine.pariente@pharmaco.u-bordeaux2.fr

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Spontaneous reporting is a valuable way to provide early detection for safety signals related to drug use.
- Due to the increasing size of pharmacovigilance databases, data-mining and other automated methods for signal generation are more and more often used.
- Even if these methods are very useful, they do not allow, for every particular association, an automated exploration of the multiple sources of confounding.

WHAT THIS STUDY ADDS

- An association between angiotensin receptor blockers use and hypoglycaemia was found in the French pharmacovigilance database.
- This signal disappeared after stratification on antidiabetic drug use, suggesting confounding by indication.
- The association between hypoglycaemia and angiotensin receptor blocker use was actually less than expected in concomitant antidiabetic drug users.

AIMS

To study reporting of hypoglycaemia in angiotensin receptor blocker (ARB) users, and to investigate the possibility of confounding.

METHODS

The French pharmacovigilance database was examined for an association between hypoglycaemia and ARBs or other drugs using reports notified between 1996 and 2005. This association was also tested in patients taking or not taking antidiabetic agents (ADAs) using reporting odds ratios (ROR).

RESULTS

Hypoglycaemia was mentioned in 807 of the 174 595 reports entered during the study period. Overall hypoglycaemia was associated with the use of ARBs [ROR 2, 95% confidence interval (CI) 1, 3] and with the use of ADAs (ROR 32, 95% CI 27, 37). Moreover, the use of ARBs was associated with the use of ADAs (OR 7, 95% CI 6, 8). Considering separately reports with and without ADA, the association of ARB use with a higher risk of hypoglycaemia disappeared (OR 0.4, 95% CI 0.2, 0.8 and OR 2, 95% CI 1, 3, respectively).

CONCLUSION

A signal indicating an association between ARB use and hypoglycaemia was found in the French pharmacovigilance database. This signal disappeared after stratification on ADA use, thus suggesting confounding by indication. Moreover, the association between ARB use and hypoglycaemia was negative in ADA users.

Introduction

In the 1990s, sporadic reports raised the hypothesis that angiotensin converting enzyme inhibitors (ACEIs) might cause hypoglycaemia [1–4], seemingly confirmed by several studies [5, 6]. Safety signals mentioning the risk of hypoglycaemia with ACEIs were promulgated. However, the mechanism of ACEI-associated hypoglycaemia was never clearly demonstrated [7]. As ACEIs are generally prescribed in hypertension and could have a nephroprotective effect in diabetic patients, this association could also result from preferential prescribing of ACEIs to diabetic patients [8]. Other studies have seemed to support this [9, 10], although a specific risk with enalapril was suspected [10].

The indications and uses of angiotensin receptor blockers (ARBs) are similar to those of ACEIs. We therefore tested the French pharmacovigilance database for a signal of hypoglycaemia associated with ARBs, using the same methodology as used previously for ACEIs in a similar context [8].

Methods

The study used data from the French pharmacovigilance database from 1996 to 2005. Reports of hypoglycaemia were taken as cases, and other reports in the database as noncases.

The cases and noncases were examined for the presence of antidiabetic agents (ADAs), ARBs, drugs used as negative (diazepam) and positive controls (cibenzoline and disopyramide) for the association with hypoglycaemia [11–14] and drugs used in the same indication as ARBs (ACEIs, calcium antagonists, diuretics, atenolol).

Statistical analysis

Cases and noncases were identified from the spontaneous adverse drug reaction reporting database. Exposure was considered as the presence in a report of the drug of interest, whether or not it was suspected of causing the reaction [8]. For each drug of interest, reporting odds ratio (ROR: ratio of the odds of exposure in reports of cases and noncases) and their 95% confidence intervals (95% CI) were computed [15]. The analysis was first performed in the whole database and then separately in reports with or without mention of ADAs.

Results

Of the 174 595 reports corresponding to the study period, 807 were of hypoglycaemia.

Table 1

Association of individual drugs with hypoglycaemia in the French pharmacovigilance database for other drugs (all reports)

	All reports	Hypoglycaemia	ROR*	95% CI†	
All reports	174 595	807	–	–	–
Any ARB‡	4 153	33	2	1	3
Losartan	1 421	12	2	1	3
Irbesartan	1 088	9	2	1	4
Valsartan	884	6	2	1	3
Candesartan	624	4	1.4	1	4
Telmisartan	124	2	4	1	14
Eprosartan	12	0	0	–	–
Diazepam	677	1	0.3	0.1	2
Disopyramide	218	16	17	10	29
Cibenzoline	180	57	107	78	148
Captopril	1 258	22	4	3	6
Enalapril	1 444	17	3	2	4
Atenolol	1 960	19	2	1	3
Nicardipine	1 393	13	2	1	4
Nifedipine	751	6	2	1	4
Nitrendipine	175	3	3	1	10
Diltiazem	1 612	12	2	1	3
Verapamil	1 032	7	2	1	3
Frusemide	7 839	93	3	2	4
Diuretics‡	4 612	45	2	1	3

*ROR, reporting 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. ‡Diuretics: thiazide and combination diuretics (cicletanine, hydrochlorothiazide, indapamide).

Angiotensin receptor antagonists and other non-antidiabetic drugs and hypoglycaemia (Table 1)

Association with any ARB in the complete database approximately doubled the overall risk of reporting hypoglycaemia. There was no clear difference between the ARBs (Table 1).

Diazepam, chosen as a negative control, was not associated with hypoglycaemia, whereas cibenzoline and disopyramide, chosen as positive controls, were.

Among the drugs sharing indications with ARBs, ACEIs (captopril or enalapril; ROR 3, 95% CI 2, 5), atenolol (ROR 2, 95% CI 1, 3), dihydropyridines (DHP) (ROR 2, 95% CI 1, 3), frusemide (ROR 3, 95% CI 2, 4) and thiazide diuretics (ROR 2.2, 95% CI 2, 3) were all associated with an increased risk of reporting hypoglycaemia in the whole database, whereas diltiazem or verapamil were not (Table 1).

Antidiabetic agents and hypoglycaemia

The ROR for hypoglycaemia with ADAs was 32 overall (95% CI 27, 37), ranging from about 4 for the glitazones (95% CI 0.5, 29) to 35 for insulin (95% CI 29, 43). It was 11 for carbutamide (95% CI 2, 85), 14 for acarbose (95% CI 10, 21), 18 for metformin (95% CI 14, 22), 21 for gliclazide (95% CI 16, 26), 32 for repaglinide (95% CI 21, 50), 46 for glibenclamide

Table 2

Association of non-antidiabetic drugs with hypoglycaemia in the French pharmacovigilance database, in reports including or not including antidiabetic agents

	All reports	Hypoglycaemia	ROR*	95% CI†	
Reports including ADAs	3 469	299	–	–	–
ARB‡	275	11	0.4	0.2	0.8
ACEI§	336	31	1	0.7	2
Atenolol	154	7	0.5	0.2	1
DHP¶	248	12	0.5	0.3	0.9
Frusemide	666	48	0.8	0.6	1
Cibenzoline	13	4	5	2	16
Reports not including ADAs	171 126	508	–	–	–
ARBs‡	2 234	10	2	0.8	3
ACEIs§	2 366	8	1	0.6	2
Atenolol	1 806	12	2	1	4
DHP¶	2 122	10	2	1	3
Frusemide	7 173	45	2.2	2	3
Cibenzoline	167	53	174	124	244

*ROR, reporting odds ratio of association of selected drug with hypoglycaemia (see Table 2). †95% CI, lower and upper limits of 95% confidence interval for OR. ‡ARBs, angiotensin receptor blockers (losartan or irbesartan). §ACEIs, angiotensin converting enzyme inhibitor (enalapril or captopril). ¶DHP, dihydropyridines (nifedipine, nicardipine, nitrendipine, nimodipine).

(95% CI 38, 56), 49 for glipizide (95% CI 31, 76) and 86 for glibornuride (95% CI 17, 446).

Association of studied drugs with ADAs

All the drugs studied except diazepam (ROR 0.7, 95% CI 0.4, 1) were associated with ADAs. Losartan was associated with ADA with an ROR of 5 (95% CI 4, 6), irbesartan with an ROR of 8 (95% CI 6, 9), captopril with an ROR of 7 (95% CI 6, 9), enalapril with an ROR of 7 (95% CI 6, 9), cibenzoline with an ROR of 4 (95% CI 2, 7), atenolol with an ROR of 4.4 (95% CI 4, 5), diuretics with an R0R of 6 (95% CI 5.5, 7), frusemide with an ROR of 5.4 (95% CI 5, 6) and DHP with an ROR of 6 (95% CI 5, 7).

Drugs other than ADAs and hypoglycaemia, according to ADA status

In reports mentioning ADAs (Table 2), none of the drugs was any longer associated with an increased risk of reporting hypoglycaemia except cibenzoline (ROR 5, 95% CI 2, 16). Actually, ARBs and dihydropyridine calcium channel blockers were associated with a reduced risk of reporting hypoglycaemia (ROR, respectively, 0.4, 95% CI 0.2, 0.8 and 0.5, 95% CI 0.3, 0.9).

In reports not mentioning ADAs (Table 2), atenolol, frusemide and cibenzoline were associated with reporting of hypoglycaemia, but not ARBs, ACEIs or DHP.

Discussion

A signal supporting an association between the use of ARBs and hypoglycaemia was generated in the French pharmacovigilance database considered as a whole. This signal disappeared after stratification on the presence of ADAs, thus suggesting confounding by indication. In fact, a decreased risk was found of reporting of hypoglycaemia in patients taking ADAs and ARBs.

Previous experience with reporting of hypoglycaemia with ACEIs had raised the possibility of confounding by indication [8], at a time when data-mining tools were not generally available. Such signals can now easily be generated by automated methods that are widely used for the detection of new adverse drug reactions. One important limitation of these methods is that they are not always able to investigate in depth potential confounding biases [16]. None explores systematically the existence of confounding by indication or channelling. This lack of adjustment could lead to false-positive signals that could modify clinical practice in inappropriate ways [17].

Our findings underline that confounding can lead to spurious disproportionality signals and suggest that special attention should be paid to eliminating the existence of such bias when considering a signal generated by automated methods using spontaneous reporting databases. They also underline the need for further research on automated signal generation, in order to develop adjustment methods that would include biases specific to pharmacoepidemiology, such as channelling or protopathic bias.

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