PHARMA EPI D EMOLOGY AN D PRESCRIPTION

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Increased reporting of adverse reactions to ACE inhibitors associated with limitations to drug reimbursement for angiotensin-II receptor antagonists

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Abstract Background and aim: From February 1998 to September 1999, the Italian Ministry of Health limited angiotensin-II type-I (AT₁) receptor antagonist reimbursement only to patients who necessitated discontinuation of angiotensin converting enzyme (ACE) inhibitor treatment due to cough or angioedema. We assessed the consequences of this decision on the reporting of ACE inhibitor-associated adverse drug reactions (ADRs).

Methods: ACE inhibitor-associated ADRs reported to the national pharmacovigilance system in 1997–2000 in the district of Varese (northern Italy, more than 820,000 inhabitants) were retrieved and analysed. The dispensation of ACE inhibitors and AT₁ receptor antagonists reimbursed by the National Health System was also examined.

Results: There were 228 reports of ACE inhibitor-associated ADRs, and cough was the ADR reported in 93.4% of cases. There were no reports of cough in 1997, 50 in 1998, 156 in 1999 and 7 in 2000. In 1998–1999, the dispensation of ACE inhibitors showed little variation, while that of AT₁ receptor antagonists grew about twofold.

Conclusions: There was a clear correlation between ACE inhibitor-associated ADR reporting and limitation to AT₁ receptor antagonist reimbursement status. Drug reimbursement policies should thus be added to the list of factors that may bias ADR reporting, and health authorities should be aware of this potential bias when defining specific measures to regulate prescription and use of new drugs.

Keywords ADR reporting · Drug reimbursement policies · Angiotensin converting enzyme inhibitors · Angiotensin-II type-I receptor antagonists

Introduction

The reporting of suspected adverse drug reactions (ADRs) by physicians is one of the mainstays of the post-marketing drug safety surveillance, its main purpose being the early generation of signals about the possible occurrence of previously unrecognised adverse events in association with the administration of drugs. Although the submission of ADR reports to the national pharmacovigilance systems is often supported by legislation and is mandatory in many countries [1], it remains primarily a voluntary decision that depends almost entirely on the individual physician’s willingness and attitude towards reporting. As a consequence, under-reporting and selective reporting represent the main limitations of spontaneous reporting systems, eventually leading to the generation of biased signals that need to be properly recognised and managed [2]. Knowledge of factors that may bias spontaneous reporting is therefore of critical importance for the analysis and interpretation of data.

Angiotensin-II type-I (AT₁) receptor antagonists are available in Italy for use in hypertension. However, as the Italian Ministry of Health considered there was inadequate data available about AT₁ receptor antagonist long-term effects and impact on morbidity and mortality in hypertension, in February 1998, their reimbursement status was limited to only those patients who necessitated discontinuation of angiotensin converting enzyme (ACE) inhibitor treatment due to cough [3]. In October 1998, the occurrence of ACE-inhibitor-induced angioedema was acknowledged as a further condition for
reimbursement of AT$_1$ receptor antagonists [4]. Limitation of the reimbursement status of these drugs was in effect until the end of 1999, when it was removed after a demand by the manufacturer which also took legal proceedings. In September 1999, a 'Dear Doctor' letter was sent by the Ministry of Health, explaining its decisions to physicians.

In the present study, we describe the occurrence of a huge number of reports of ACE-inhibitor-induced cough to the national pharmacovigilance system in close coincidence with the limitation to AT$_1$ receptor antagonist reimbursement status. During the same period, the dispensation of ACE inhibitors increased only slightly, while that of AT$_1$ receptor antagonists grew about twofold. Limiting drug reimbursement to those conditions in which ADRs to other drugs occur may profoundly affect ADR reporting rates, and it should thus be included among the factors not related to the actual safety profile of drugs which nevertheless are likely to produce biased signals in pharmacovigilance.

**Methods**

Spontaneous reports of ACE inhibitor-associated ADRs were retrieved from the ADR report database of the Area Health Authority (AHA, the basic unit of the Italian national health system which also holds the responsibility to manage the national pharmacovigilance system in general practice at the local level) of Varese, a district in northern Italy where more than 820,000 inhabitants live. Since the Italian national pharmacovigilance system was reorganised at the beginning of 1997, we scrutinised the reports received from January 1997 onwards. Information contained in the selected reports was transferred to an electronic data sheet and analysed.

Data concerning the dispensation of drugs reimbursed by the National Health System were obtained from the prescription pricing regional system, and the numbers of defined daily doses (DDDs) per 1,000 inhabitants per day of ACE inhibitors and of AT$_1$ receptor antagonists dispensed in the territory of the AHA of Varese in 1998–1999 were calculated using the ATC index with DDDs [5].

**Results**

Between January 1997 and December 2000, a total of 228 ADRs related to ACE inhibitor administration were reported by general practitioners to the AHA of Varese. There were 213 (93.4%) reports of cough with ACE inhibitors. Other reports described angioedema (3, 1.3%), erythema (3, 1.3%), erectile dysfunction (2, 0.9%) and other ADRs (7, 3.1%). There were 50 reports of cough in 1998 (23.5%), 156 in 1999 (73.2%) and 7 in 2000 (3.3%). No reports were sent in 1997. It may be noteworthy that all 1998 reports were received from April onwards and all 1999 reports were received before the end of September (i.e. only when the limitation to AT$_1$ receptor antagonist reimbursement was in force).

The annual reporting rate of ACE-inhibitor-induced cough was thus (reports/10$^6$ inhabitants × year) 0 in 1997, 61 in 1998 (or 81 in April–December, when all the reports were received), 190 in 1999 (or even 253 in January–September, when all the reports were received), and 9 in 2000. Figure 1 shows the time course of the reports of cough on a monthly basis.

There were 23 physicians reporting ACE-inhibitor-induced cough in 1998 (mean ± SD reports/physician 2.17 ± 1.27; min–max 1–5), 47 in 1999 (3.21 ± 3.48; 1–19), and 4 in 2000 (1.75 ± 0.96; 1–3). Patients involved were 62% females (mean ± SD age 67.20 ± 10.97 years; min–max 34–92 years) and 38% males (61.32 ± 11.04 years; 33–86 years); the ratio of female/male was 1.64. The main indication for ACE inhibitor use was hypertension (98.1% of reports). The duration of exposure before onset of cough was indicated in 145 reports (69.0% of total reports of cough) and ranged from 1 day

**Fig. 1** Time course of the reports of ACE inhibitor-associated cough and limitation to AT$_1$ receptor antagonist reimbursement status.

![Graph showing time course of reports of ACE inhibitor-associated cough](image_url)