Under-reporting of adverse drug reactions in general practice

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Aims In post-marketing setting, spontaneous reporting by physicians is a mode of surveillance of adverse effects associated with drug use. The objective of this study was to quantitatively assess under-reporting of adverse drug reactions (ADRs) in general practice.

Methods A random sample of 100 general practitioners (GPs) practising in the region of the Bordeaux pharmacovigilance centre were surveyed to obtain data on adverse effects observed. Overall, 81 GPs agreed to record during 3 non-consecutive working days any effect they believed to be associated with drug use. The types of effects, regardless of their seriousness and labelling, and the drugs suspected were characterized and compared to spontaneous reports received from GPs by the Bordeaux pharmacovigilance centre during the reference period.

Results The average number of ADRs observed per day per GP was 1.99. The estimate of the under-reporting coefficient (U) was 24 433 (95% confidence interval: 20 702–28 837) which indicates that, as a whole, GPs might be expected to report only 1 out of every 24 433 ADRs to the pharmacovigilance centre. Under-reporting was lowest for serious and unlabelled effects (U=4610; 95%CI: 2514–8454) and for drugs marketed recently (U=12 802; 95% CI: 8174–20 050).

Conclusions Adverse effects due to drugs are part of GPs routine activities. According to the observed trend in under-reporting, there appears to be a selection process which indicates that spontaneous reporting in general practice is not conducive to an exhaustive description of the safety profile of a drug. However, our findings are consistent with greater efficacy of spontaneous reporting in detecting serious and unlabelled effect.

Keywords: adverse drug reactions, pharmacovigilance, spontaneous reporting

Introduction

In post-marketing setting, spontaneous reporting is a mode of surveillance of adverse effects possibly related to the use of medicines in a well-defined geographical region. It is achieved by physicians who voluntarily report any effect they believe to be attributable to a drug taken by the patient. The French pharmacovigilance system was implemented in 1973 and spontaneous reporting was made mandatory for all prescribers in 1984. This system consists of 30 regional centres which are under the supervision of a coordinating committee at the French Drug Agency. In addition to receiving, assessing and recording systematically spontaneous reports, one role of the regional centres is to act as information providers to the health professionals [1]. The total number of suspected adverse drug reactions (ADRs) received is approximately 10 000 per year [2]. Due to its passive nature, data collection is not exhaustive as it depends on the motivation of physicians to report. Hence, some ADRs, even if observed, are likely not to be reported to the pharmacovigilance system.

The magnitude of under-reporting is unknown which precludes knowledge of how many cases of ADRs have really occurred. Furthermore, physicians may select the types of effects they report: the set of reported cases may be non-representative of all the cases that really occurred, in terms of seriousness, novelty of the drug or the effect, and groups of users [3]. It has been found that serious and unexpected ADRs or those associated with newly marketed drugs are more likely reported [4, 5]. Under-reporting may lead to failure to detect an unacceptable risk associated with a given drug [6]. Furthermore, the extent of under-reporting may differ between drugs and thus may lead to apparent differences in toxicity which are spurious [7]. So far, the effect of under-reporting on the risk estimates have mainly been addressed theoretically.

Studies found in the literature have addressed under-reporting of ADRs in outpatient [4, 8] as well as inpatient settings [9]. In these previous studies, a global approach was used to evaluate the pharmacovigilance system as a whole, irrespective of the reporting sources. Although ADRs observed by GPs have been studied in the Lumley *et al.* study [4], under-reporting was not assessed specifically for reports originating from GPs. The objective of the present study was to assess the magnitude of under-reporting by GPs for ADRs that occur in general practice setting. In order to address this issue, we attempted to provide a

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quantitative assessment of the under-reporting of ADRs and to compare its magnitude between types of ADRs and drug classes.

Methods

For this study, we defined an adverse effect as any unintended and noxious effect, whatever its seriousness and labelling, perceived by the prescriber as being possibly related to a drug treatment.

Under-reporting was quantified by the under-reporting coefficient, U, which is the ratio between the number of effects actually observed by physicians divided by the number of effects spontaneously reported to the pharmacovigilance system in the same catchment area and time period [10]. Data on the effects observed by physicians were obtained by surveying general practitioners (GPs) and data on spontaneous reports were retrieved from the Bordeaux pharmacovigilance centre database.

A sample of 100 GPs was randomly selected from a register which included the 5009 GPs practicing in the catchment area of the Bordeaux pharmacovigilance centre. Selected GPs were representative of the GP population in terms of age, gender and year of graduation. They were contacted by mail to seek their participation. Those who agreed were asked to record in a specific booklet all adverse events they believed to be associated with drugs, during a whole day of practice, once a month during 3 consecutive months (April, May, June 1993). In contrast to the standard spontaneous reporting form used at the Bordeaux pharmacovigilance centre, the amount of information to be supplied in the survey booklet was limited in order to maximise GPs' participation: age, gender, adverse effect and suspected drugs. GPs were instructed that any effect had to be recorded regardless of seriousness, labelling or novelty of the drug.

Spontaneous reports used as the reference were those spontaneously sent to the Bordeaux pharmacovigilance centre by all GPs practicing in the catchment area ($n=$ 5009) for a period of 1 year (July 1st, 1992 to June 30th, 1993).

Suspected drugs were classified into broad therapeutic classes following the Anatomical Therapeutic Chemical (ATC) classification system [11]. Adverse effects were categorised into system organ classes according to the World Health Organisation (WHO) adverse reactions terminology [12]. Multiple ADRs occurring in the same patient during the same visit were considered as a single observation. An effect was referred to as serious only if it appeared in the list of critical terms proposed by the WHO [13], without consideration of its intensity or consequences (e.g. life-threatening, hospital admission etc.). The effect was considered to be labelled if it was mentioned in the 1993 French drug compendium [14]. In order to assess trends in under-reporting, ADRs were classified according to seriousness, as defined by the WHO list of critical terms, as well as labelling. Four classes were used: 1) serious and unlabelled, 2) serious and labelled, 3) non-serious and unlabelled, 4) non-serious and labelled. An arbitrary criterion was used to assess the novelty of a drug: drugs first marketed in 1991 or later were considered as new.

For both the GP survey and the spontaneous reports, the following data were retained for the study: GP's identification number, observation number, patient's age and gender, ADRs observed (maximum 3), suspected drugs (maximum 2 per effect).

Estimation of the under-reporting coefficient

The under-reporting coefficient (U) was calculated as follows:

$$U=\frac{m}{k\times n/N}$$

where: $m=$number of ADRs observed in the GP survey; $n/N=$sampling fraction (number of GP-days in the sample survey divided by the total; number of GP-days in the catchment area); $k=$number of ADRs spontaneously reported.

The total number of GP-days (N) was derived from the total number of GPs in the catchment area of the Bordeaux pharmacovigilance centre (5009) and the average number of days worked by each GP during the year (estimated by surveying 40 GPs).

Estimation of the confidence interval for the under-reporting coefficient

The uncertainty associated with the estimate of the under-reporting coefficient was quantified by the 95% two-sided confidence interval (CI). The total number of reports received from GPs by the pharmacovigilance centre (k) was considered fixed and m was assumed to follow a Poisson distribution because the probability of occurrence of an ADR is small and the population surveyed is large. In order to take into account the uncertainty due to the sampling of GP-days, the sampling fraction was not considered as fixed and the 95% CI was first calculated for $m/(n/N)$ according to the δ-method of large sample theory [15]:

$$\exp\{\ln(m/(n/N))\pm 1.96\sqrt{1/m+1/n+1/N}\}$$

where $\ln(x)$ is the natural logarithm of x.

The upper and lower bounds were subsequently divided by the constant k to obtain the 95% CI for U.

Descriptive analyses were conducted on both survey and spontaneous reporting data. The significance of any heterogeneity was assessed by the chi-square test and the significance level set at 0.05. All statistical analyses were conducted using the SAS statistical package [16].

Results

Out of the 100 GPs who were initially contacted, 81 (81%) agreed to participate in the survey. A total of 210 observation-days (n) were collected over the 3-month period, and 419 ADRs were observed. The mean number of ADRs observed per GP on a given day was 1.99 (median: 2; range: 0–8). The women to men ratio for patients who experienced an ADR was 1.55 and the mean age of patients was 57.3 years (range $=<1$–97 years). Out of the 835 spontaneous reports received by the Bordeaux pharmacovigilance centre for a period of 1 year, 115 (13.8%) originated from GPs. Patients included in spontaneous reporting were

Table 1 Serious ADRs, as defined by the WHO critical terms list [13], observed in the GP survey and serious ADR spontaneous reports to the Bordeaux pharmacovigilance centre 1992–93

Serious adverse drug reaction	*GP survey number*	*Spontaneous reports (number)*
Gastrointestinal bleeding	4	–
Colitis	1	–
Stevens-Johnson syndrome	–	1
Photosensitivity reaction	2	1
Abnormal renal function	3	–
Abnormal vision	3	1
Hallucination	2	6
Drug addiction	2	1
Hypertension	1	2
Arrhythmia	–	1
Hepatocellular damage	1	5
Aplastic anaemia	1	–
Coagulation disorder	–	3
Anaphylactic shock	–	1
Seizure	1	–
Myopathy	–	1
Total	21	23

slightly younger than those of the survey (mean of 52.8 *vs* 57.3 years old) and the female to male ratio was 1.17.

Serious effects, as defined by the WHO critical terms list, observed in the GP survey and spontaneous reports are listed in Table 1. Out of all ADRs observed in the survey, 21 (5.0%) were considered to be serious while 23 serious effects were reported to the pharmacovigilance centre, which accounted for a significantly greater proportion of reports (20.0%) ($P<0.001$).

As shown in Table 2, most effects observed in the GP survey were non-serious and labelled (69.5%). Unlabelled effects accounted for a smaller proportion of ADRs in the GP survey than in spontaneous reporting (28.2% *vs* 58.3%, $P<0.001$). The distribution of effects into the seriousness-labelling categories in the GP survey and spontaneous reports was heterogeneous ($P<0.001$). In particular, spontaneous reports involved a greater proportion of serious and unlabelled effects (13.9% *vs* 2.6%, $P<0.001$).

The number of ADRs associated with drugs marketed since 1991 was 21 in the survey (5.0% of suspected drug classes) and 11 in the reports sent to the pharmacovigilance centre (9.6%) (non-significant difference).

Types of adverse effects

The majority of effects observed in the GP survey involved the gastrointestinal (GI) tract (34.6%), which consisted mainly of diarrhoea and epigastric pain. Neurological disorders came second (15.5%) followed by skin disorders (10.7%). In contrast, skin disorders were the most frequently reported spontaneously to the pharmacovigilance centre (22.6%), followed by psychiatric and neurological effects (14.8% and 12.2%, respectively). In both the survey and the spontaneous reports, the other observations were distributed similarly across many types of ADRs.

Drug classes

Cardiovascular drugs were the most frequently suspected in the survey (27.0%), followed by those prescribed for the central nervous system (17.9%). Similarly, the latter were among the most frequently suspected in reports sent to the pharmacovigilance centre (23.5%) followed by anti-infectives (19.1%).

Estimation of the under-reporting coefficient

The average number of working days per GP per year, estimated by surveying 40 GPs, was 281.13 (including on-call duties). Based on the total number of GPs in the catchment area (5009), the total number of GP-days for a 1-year period (N) was estimated to be 1.41×10^6. Given that the total number of GP-days in the survey was 210, the sampling fraction (n/N) was 1/6706.

Using the formula described above, the under-reporting coefficient (U) for all types of ADRs combined was 24 433 (95% CI: 20 704–28 837), which means that only 1 out of every 24 433 ADRs observed by GPs in the entire population over a period of 1 year would be reported. The under-reporting coefficient for serious, as defined by the WHO critical terms list, and unlabelled effects was 4 610 (95% CI: 2 514–8 454) which is approximately 10 times lower than for non-serious and labelled effects (47 596; 95% CI: 39 856–56 839) (Table 2). The under-reporting coefficient for newly marketed drugs was 12 802 (95% CI:

Table 2 Distribution of adverse drug reactions according to seriousness-labelling categories for GP survey and spontaneous reporting data

*Seriousness-labelling category**	*GP survey number (%)*	*Spontaneous reports number (%)*	*Under-reporting coefficient (95% CI)*
1. Serious and unlabelled	11 (2.6)	16 (13.9)	4610 (2514–8454)
2. Serious and labelled	10 (2.4)	7 (6.1)	9580 (5080–18 067)
3. Non-serious and unlabelled	107 (25.5)	51 (44.3)	14 069 (11 147–17 758)
4. Non-serious and labelled	291 (69.5)	41 (35.7)	47 596 (39 856–56 839)
Total	419	115	24 433 (20 702–28 837)

* Serious as defined by the WHO critical terms list.
Labelled as defined by the mention of the ADR in the 1993 French drug compendium.

8 174–20 050), which was approximately half that of all drugs combined.

Because of the random selection process, 15 GPs who participated in the survey (18.5%) had also sent reports to the Centre during the reference period, and accounted for 36 of the total of 115 spontaneous reports (31.3%). These GPs were also keen to participate in the survey as 13 of them completed the 3 days of observation. Overall, out of the 81 participating GPs, 61 (75.3%) completed the 3 days of observation. For them, the mean number of ADRs observed was 6.2 (s.d. = 4.1; median = 5; range: 1–21). Most did not report to the Centre, but those who did (13/61) sent on average 2.7 reports during the year (median = 1; range: 1–13). The association between reporting at least once to the Centre during the reference period and observing a large number of ADRs during the 3 days of practice (above the 90th percentile of the distribution of observed ADRs) was not significant (chi-square = 1.735, $P = 0.311$). Four GPs observed a large number of ADRs during those 3 days (21, 13, 11 and 11, respectively) but they do not usually report them, as shown by the absence of spontaneous reports from them during the reference period. In order to determine if such GPs could bias the results, U was estimated without including these outliers. The estimate was 22 478 (95% CI: 18 904–26 727), which was similar to the overall estimate of under-reporting coefficient ($U = 24\,433$).

Discussion

This study attempted to quantify the extent of under-reporting of ADRs associated with drug use in general practice. It was shown that under-reporting is very marked among French GPs despite a particularly well developed and established pharmacovigilance system [17]. Nevertheless, results confirmed intuitive hypotheses found in the literature that under-reporting varies with types of ADRs and drugs. Serious ADRs, as defined by the WHO critical terms list, and effects involving drugs marketed recently were more frequently reported. Under-reporting was lowest for serious and unlabelled effects but even so, only 1 out of 4610 of these effects would be reported. Although this study did not intend to address global under-reporting, these findings in general practice setting are consistent with greater efficacy of spontaneous reporting in detecting serious effects in a timely manner after a drug has been marketed. However, despite this trend, the absolute level of under-reporting is very marked even for serious effects. As mentioned previously, only effects appearing in the WHO list of critical terms were considered, irrespective of intensity or consequences. This may greatly differ from effects that are perceived by GPs to be serious and thus more likely reported to the pharmacovigilance system.

The heterogeneity in the magnitude of under-reporting shows that a single estimate of U cannot be used as a correction factor in the estimation of the reporting rates associated with a given drug. Similarly, in the comparison of toxicity between drugs, our results suggest that spurious findings may be found if the magnitude of under-reporting is drug-specific [7]. For instance, great caution should be taken when comparing a new drug with an older drug of the same therapeutic class. On the basis of these considerations, spontaneous reporting by GPs only does not appear adequate for an exhaustive description of the safety profile of a drug used in community setting.

It is interesting to note that the types of effects observed by GPs in our study were very consistent with results found by Lumley and colleagues [4] despite geographical, temporal and methodological differences between the two research settings. The ADRs most frequently observed were gastrointestinal (34.6% and 31%, respectively for the present study and that by Lumley), followed by neurological (15.5% and 20%) and dermatological (10.7% and 11). Similarly, cardiovascular drugs were the most frequently suspected in the two studies (27% and 23%, respectively for each of the two studies).

Because in the survey GPs were asked to report any ADR even if mild and well-known, many mild disorders such as nausea and abdominal discomfort were included as observations. These are normally not reported to a pharmacovigilance centre. This is appropriate because if all these mild effects were reported, they would overwhelm the system, which would not be useful for alert situations where only serious effects are important. On the other hand, spontaneous reporting should not be restricted to the detection of rare and serious ADRs. This system is also useful to detect non-serious but unlabelled ADRs, as previously seen with cough induced by ACE inhibitors [3].

A limitation of the study is the small sample size, which led to a very small sampling fraction. Even so, a few serious effects (e.g. renal failure, hypertension and gastrointestinal bleeding) were observed. To increase the sampling fraction would have been prohibitive. For example, 5% of GP-days (70 500 GP-days) would have required the participation of 1 500 GPs once per week during 47 weeks, which was deemed not feasible. Because the survey involved GPs who volunteered to participate, two potential sources of biases may be considered: i) the prescription habits of these GPs could be at lower risk for an ADR than those of the other GPs, ii) these GPs may not be representative of all GPs in their judgment to associate an effect to a drug. The first bias would result in an under-estimation of the under-reporting coefficient since less ADRs would be expected to occur and to be observed. In contrast, the second source of bias would lead to an over-estimation of under-reporting if participating GPs detected more drug-effect associations because their attention was prompted by the study. This would result in a higher value of the numerator of the estimator U.

It may be hypothesized that GPs who report to the Centre tend to also observe more ADRs, which could bias the results by over-estimating the number of observed ADRs per day of activity. However, in our study, there was no association between reporting at least once to the Centre during the reference period and observing a large number of ADRs during the 3 days of practice.

Estimates of the under-reporting coefficient obtained in this study are only generalizable to reports made by GPs in this pharmacovigilance system. Factors that may influence reporting is the extent of information required (reporting form) and physician's awareness. This study shows that under-reporting of ADRs is an unavoidable reality in a context where adverse drug reactions are part of GPs routine

activities. According to our results, a GP observes on average two ADRs per day of practice and reports less than 0.02 per year (115/5009). Other studies have found under-reporting to vary between 90% and 98% [4, 18, 19]. Under-reporting estimated in the present study is very marked and much higher than these previous figures. The difference between findings can largely be attributed to the sources of reports as previous studies considered spontaneous reports from all sources as opposed to only those sent by GPs. However, it must be kept in mind that pharmacovigilance extends beyond GP routine practice. In fact in our centre, GPs contribute only 13.8% of all reports which differs markedly from the UK yellow card system for example, where half of the reports originate from GPs [20]. Another study conducted in the UK found that GPs accounted for only 10% of serious and non-fatal reactions [21]. Although under-reporting is very marked among GPs, population-wide the average reporting rate in France (from all sources including the pharmacovigilance system and industry) is 388 reports per million inhabitants per year. These findings are consistent with other countries such as the USA where the reporting rate is 205 per million, the United Kingdom (383 per million) and Germany (409 per million) [17].

In their reports, GPs favour serious and/or unlabelled ADRs as well as those suspected to be due to newer drugs. This selection process is desirable in order to avoid overwhelming the system with numerous known and non-serious effects. Extrapolating to the total number of GPs included in the catchment area of this study, 2.82 million ADRs would have been expected during a whole year of general practice in a population of 3.6 million inhabitants. Fortunately, there is an important trend for the most relevant ones to be reported.

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