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The Influence of Primary Care Prescribing Rates for New Drugs on Spontaneous Reporting of Adverse Drug Reactions

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Abstract

Introduction: Adverse drug reaction (ADR) reporting makes a vital contribution to pharmacovigilance, although the factors that influence the reporting rate remain unclear. The aim of this study was to investigate whether the variation in the rate of reporting of suspected ADRs in different regions of Scotland was explained by differences in local prescribing practice and to quantify the extent of this influence.

Methods: Population and primary care prescribing data were obtained for ten geographical areas based on the 15 administrative regions of the National Health Service in Scotland. All reports of suspected ADRs received from within Scotland for 2000 and 2001 were available from the regional monitoring centre (Committee on Safety of Medicines, Scotland). The primary analysis was based on 14 medications that appeared in the 'top ten' list for the frequency of reported ADRs for either year. Reporting rates for each area were expressed both in terms of population (reports per million people) and in terms of estimated exposure to those medications in primary care (reports per 1000 prescriptions). For each analysis, the Pearson correlation coefficient between reporting and prescribing data was calculated using SPSS™ software.

Results: The 'top ten' medications accounted for 1715 of 2817 (60.9%, 95% CI 59.1, 62.7) ADR reports but only 2.2 million out of a total of 128 million primary care prescriptions (1.7%). Although there was a 3-fold geographical variation in the per-population ADR reporting rate, there was a close correlation between local reporting of ADRs and prescribing of the index medications ($p = 0.66$, $p = 0.04$,

respectively). This implies that 44% of the observed variation in reporting rate can be attributed to variation in prescribing within the same population.
Discussion: Spontaneous ADR reporting in Scotland over the 2 years studied was highly concentrated on a small number of medications that were under intensive surveillance. Although there was a 3-fold variation in reporting rates from individual geographic areas when corrected for the size of the population, primary care prescribing data showed nearly half of this local variation in reporting rates could be explained by differences in prescribing. This study highlights the importance of considering prescribing practice when interpreting spontaneous ADR reporting data.

Spontaneous reporting of adverse drug reactions (ADRs) by healthcare professionals is an important component of pharmacovigilance. It provides early warnings about safety issues concerning new medications, to which only a few hundred patients may have been exposed prior to the authorisation to prescribe within the wider population.[1] In the UK, spontaneous reports of ADRs are made using 'yellow cards', which are collected by the Committee on Safety of Medicines (CSM), an advisory body of the Medicines and Healthcare products Regulatory Agency.

It is widely recognised that ADRs are underreported and that reporting is selective and biased towards newer products for which intensive reporting is encouraged.[2,3] Spontaneous reporting data are often presented with a population denominator,[4] but this does not take into account other important factors that might influence reporting within individual populations. Perhaps the most important of these is the variation in the rates of exposure to the particular medications; with some limitations, the number of prescriptions is a reasonable proxy for the number of people exposed.[4-6] However, it is not known whether prescribing rates influence the spontaneous reporting rates for a particular medications or group of medications.

The aim of this study is to investigate the hypothesis that the variation in the rate of reporting of suspected ADRs in different regions of Scotland is explained by differences in local prescribing practice and to try to quantify this influence. This was achieved by comparing data on ADR reports received by the CSM from throughout Scotland with primary care prescribing data.

Methods

Data Sources

Population data at health board level were obtained from the General Register Office for Scotland based on the population estimated in the 2001 census. CSM data for ADR reports were aggregated into ten geographic areas based on the 15 administrative regions of the National Health Service (NHS) in Scotland (this involved the amalgamation of some small populations) [table I]. Two health boards with the smallest populations were omitted from the analysis because no reports of suspected ADRs had been received from them during the study period.

Data on prescribing were obtained from the Practitioner Services Division of the Common Services Agency of the NHS in Scotland, which undertakes prescription pricing for all dispensed NHS prescriptions originating from primary care in Scotland. These data include the drug, formulation, strength, quantity and cost but do not historically include patient details, information on the dose prescribed,

Table I. The total population in each geographical area listed in order of population size

Health board code	Population[a]
A	2 210 390
B	779 000
C	525 850
D	388 750
E	349 690
F	279 240
G	208 920
H	147 780
I	106 950
J	26 450
Total	5 023 020
Scotland	5 064 200

a The population figures given are from a mid-year estimate for 2001 taken from the General Register Office for Scotland, based on the 2001 census. Two health boards with the smallest populations were omitted from the analysis because no reports of suspected ADRs had been received from them during the study period. Therefore, the total of the health boards listed is slightly less than that for Scotland.

the diagnosis for which the prescription is written or the duration of treatment.

In the UK, healthcare professionals are encouraged to report all serious ADRs to any medicine and any ADR to a subset of newer medicines that remain under intensive surveillance; these are known as black triangle drugs because of the symbol that highlights them in the British National Formulary. All reports of suspected ADRs received by the CSM from within Scotland for 2000 and 2001 were available from the database of its regional monitoring centre (CSM Scotland). Each report was coded according to the date of receipt, patient age, medication under suspicion, nature of the reaction, patient outcome, classification of the reaction as 'serious' or 'non-serious' according to predefined criteria, black triangle status and the reporting health board. From these data, a list of 'top ten' medications that most frequently had ADRs reported in each year was compiled. Reporting rates for these medications were calculated for each health board.

Two 'top ten' preparations were excluded from the analysis of prescribing. Capecitabine (37 reports in 2001) is used in the treatment of cancer and is prescribed and supplied almost exclusively in secondary care, therefore no primary care prescribing data were available. Meningococcal group C vaccine (1092 reports in 2000 and 22 in 2001) was incorporated into the UK childhood immunisation programme in 1999 and is distributed under centrally co-ordinated arrangements and this supply does not appear in prescribing data.

Statistical Analysis

The primary analysis was based on prescribing and reporting data for the 'top ten' medications for ADR reports, combined for 2000 and 2001. Secondary analyses were undertaken for data relating to individual years and individual drugs. The number of CSM reports was further expressed both in terms of population (reports per million people) and in terms of exposure to those medications in primary care (reports per 1000 prescriptions) at each level of aggregation. The primary measure chosen to investigate any association between reporting and prescribing was the coefficient of correlation and associated p-value for the number of reports to the CSM from Scotland per million population and the number of primary care prescriptions per 1000 population ('top ten' medications, 2 years' data combined). To take into account the possibility that the largest health board (comprising 44% of the total population studied) could have a disproportionate influence on correlation coefficients, a further analysis was conducted for the primary measure excluding this health board.

Correlation coefficients and associated p-values were also calculated at other levels of aggregation, such as for all prescriptions, all reports, for individual years and, as an exploratory analysis, for individual 'top ten' products. For each analysis of correlation, SPSS™ software was used to produce a scatter

diagram, with reporting data as the y-axis and prescribing data as the x-axis, a Pearson correlation coefficient and a p-value based on the t-test. A Spearman correlation coefficient with associated p-value from a non-parametric test was also calculated, if linearity was not clear from the scatter diagram. A p-value of ≤0.05 was considered statistically significant. However, for single-year analyses, where the measure of association was estimated for both 2000 and 2001, a Bonferroni correction was applied, giving a level of significance for each year ≤0.025.

Results

Reporting and Prescribing Rates for Top Ten and Black Triangle Medications

The total number of ADR reports was 2513 in 2000 and 1455 in 2001, the excess for 2000 resulting from intensive reporting associated with the meningococcal group C vaccine. Of all the reports for these years, 35% were classified as 'serious'. A total of 16 medications appeared in the top ten list for either 2000 or 2001, the primary systems affected by which are shown in table II. When combined, the top ten medications accounted for 1959 (78%) reports in 2000 and 907 (62%) in 2001, equivalent to 72% of all reports for both years combined. After excluding ADR reports associated with meningococcal group C vaccine and capecitabine, the proportion of total ADR reports that were associated with top ten medications for both years combined was 1715 of 2817 (60.9%; 95% CI 59.1, 62.7) with proportions of total reports ranging from 47.4 to 88.3% for individual health boards.

The number of primary care prescriptions for the top ten medications was 1 million in 2000 and 1.2 million in 2001. Since the total number of prescriptions (all medications) in Scotland was about 62.2 million in 2000 and 65.4 million in 2001, this was equivalent to 1.72% (95% CI 1.716, 1.720) of all prescriptions being for top ten medications for the 2 years combined. The proportions of all prescriptions that were for the top ten medications ranged from 1.26 to 2.10% across health boards.

Table II. Distribution of black triangle[a] products and top ten[b] medications across therapeutic categories

Category	Number of medications	
	black triangle	top ten
CNS	40	8
Cardiovascular	34	2
Malignant disease and immunosuppression	31	1
Infections	27	
Endocrine	21	1
Topical (eye, ear, nose, throat, skin)	21	
Nutrition and blood	12	
Immunological products and vaccines	12	1
Respiratory system	10	
Musculoskeletal and joint	10	3
Obstetrics and gynaecology, urinary tract disorders	9	
Gastrointestinal	8	
Anaesthesia	4	

a In the UK, healthcare professionals are encouraged to report all serious adverse drug reactions (ADRs) to any medicine and any ADR to a subset of newer medicines that remain under intensive surveillance, known as black triangle drugs because of the symbol that highlights them in the British National Formulary.

b In terms of the number of adverse drug reaction reports to the Committee on Safety of Medicines from Scotland.

A total of 239 products had black triangle status for at least part of the study period (including all of the top ten medications), of which prescribing data were available for 117. There were 3 million prescriptions for these products in 2000 and 4.2 million in 2001, equivalent to 4.8% and 6.5%, respectively, of primary care NHS prescribing in Scotland overall, and 5.6% for the 2 years combined. After exclusion of meningococcal group C vaccine and capecitabine, the top ten medications accounted for 30.7% of prescriptions for black triangle products for the 2 years combined. The remaining black triangle medications, for which data were unavaila-

Table III. Number of reports of suspected adverse drug reactions (ADRs) and prescriptions dispensed in primary care, and ADR reporting rates per million population and per 1000 prescriptions in Scotland for 2000 and 2001 combined

	No. of ADR reports	No. of prescriptions (000s)[a]	Mean ADR reports per million population[b] (95% CI)	Mean ADR reports per 1000 prescriptions (95% CI)
Top ten medications[c] for which prescribing data were available	1 715	2 208	341 (290, 392)	0.78 (0.66, 0.89)
All medications prescribed	3 968	127 582	790 (713, 868)	0.031(0.028, 0.034)

a The number of prescriptions refers to primary care prescribing within the National Health Service in Scotland.

b Calculated using the sum of the 2001 mid-year estimates of the population sizes for the ten included health boards, taken from the General Register Office for Scotland and based on the 2001 census.

c In terms of the number of adverse drug reaction reports to the Committee on Safety of Medicines of Scotland and excluding capecitabine and meningococcal group C vaccine.

ble, were either short-term hospital-only drugs or drugs that were administered on the basis of centrally driven protocols e.g. vaccines.

Relationship between Reporting and Prescribing Rates

Table III and table IV show the number of prescriptions and numbers and rates of ADR reports (expressed in terms of population and prescription numbers) for all medications, all top ten medications and individual top ten medications. There was a highly significant correlation between the number of ADR reports associated with top ten medications for each health board and the number of prescriptions for top ten medications ($p = 0.995$, $p < 0.001$, respectively). The correlation between the number of ADR reports and the number of prescriptions was also found at other levels of data aggregation, and observed for a number of individual top ten drugs. However, significant correlations also existed between the number of reports and the population size (e.g. $p = 0.97$, $p < 0.001$) and between the number of prescriptions and the population size ($p = 0.98$, $p < 0.001$, respectively). Thus, population size was clearly a major confounding factor that influenced both the number of prescriptions and the number of ADR reports. Therefore, the primary measure chosen to investigate the association between reporting of ADRs and prescribing of medication was the coefficient of correlation between the number of ADR reports to CSM Scotland per million population and the number of primary care prescriptions per 1000 population (top ten medications, 2 years combined).

When the rates of ADR reporting to the CSM for the top ten medications were expressed as the number of reports per million population, combined for 2000 and 2001, the range between health boards was 186–663 and the mean across health boards was 349 (95% CI 297, 401) [figure 1a]. When expressed as the number of reports per 1000 prescriptions at the same level of aggregation, the range was 0.66–1.48, with a mean of 0.78 (95% CI 0.66, 0.89) [figure 1b]. For all reports to the CSM, the range for reports per million population across health boards was from 438 to 1473 with a mean of 790 (95% CI 713, 868). For reports per 1000 prescriptions, the range was 0.022–0.059 and the mean was 0.031 (95% CI 0.028, 0.034). For the primary outcome measure, there was significant correlation between the number of ADR reports per million population and the number of prescriptions per 1000 population ($p = 0.66$, $p = 0.04$, respectively) [figure 2]. This implies that 44% of the observed variation in reporting rate can be attributed to variations in prescribing rate within the same population. After exclusion of the largest health board, the correlation increased slightly and remained significant ($p = 0.74$, $p = 0.02$,

Table IV. Prescription and adverse drug reaction (ADR) report data for individual 'top ten'[a] medications in Scotland

Drug	Year	No. of ADR reports	No. of prescriptions (000s)	Mean ADR reports per million population[b]	Mean ADR reports per 1000 prescriptions
Buproprion	2000	494	45	98	11.0
	2001	532	41	106	13.0
Rofecoxib	2000	143	115	28	1.2
	2001	92	214	18	0.4
Celecoxib	2000	22	17	4	1.3
	2001	80	115	16	0.7
Venlafaxine	2000	44	157	9	0.3
	2001	38	211	8	0.2
Citalopram	2000	32	252	6	0.1
	2001	22	348	4	0.1
Clopidogrel	2000	26	35	5	0.7
	2001	21	83	4	0.3
Mirtazapine	2000	36	44	7	0.8
Donepezil	2001	31	12	6	2.6
Reboxetine	2000	24	14	5	1.7
Leflunomide	2001	24	5.2	5	4.6
Alendronic acid	2001	23	100	5	0.2
Gabapentin	2000	23	32	5	0.7
Atorvastatin	2000	23	306	5	0.1
Olanzapine	2001	22	61	4	0.4

a In terms of the number of adverse drug reaction reports to the Committee on Safety of Medicines of Scotland and excluding capecitabine and meningococcal group C vaccine.

b Calculated using the sum of the 2001 mid-year estimates of the population sizes for the ten included health boards, taken from the General Register Office for Scotland and based on the 2001 census.

respectively). For individual medications, there were statistically significant positive correlations between the number of ADR reports per million population and the number of prescriptions per 1000 population when health board data for buproprion, rofecoxib, citalopram and clopidogrel (2000 and 2001 combined) were considered (table V).

Discussion

The main findings of this study are that (i) spontaneous ADR reporting in Scotland over the 2 years studied was highly concentrated on a small number of medications with black triangle status; (ii) there was a 3- to 4-fold variation in reporting rates from individual areas when corrected for the size of the population; and (iii) nearly half of this local variation in reporting rates could be explained by differences in prescribing rates.

A recognised limitation of spontaneous ADR reporting data is the lack of information that links the reporting rate to the extent of exposure to the product suspected of causing the ADR.[5,6] This study investigated the potential benefits of adding prescribing data to reporting data in Scotland and two approaches were used. The first was to examine the variation in health board reporting not explained by variation in population size, and the second was to focus on the small number of medications (the 'top ten') that dominated reporting.

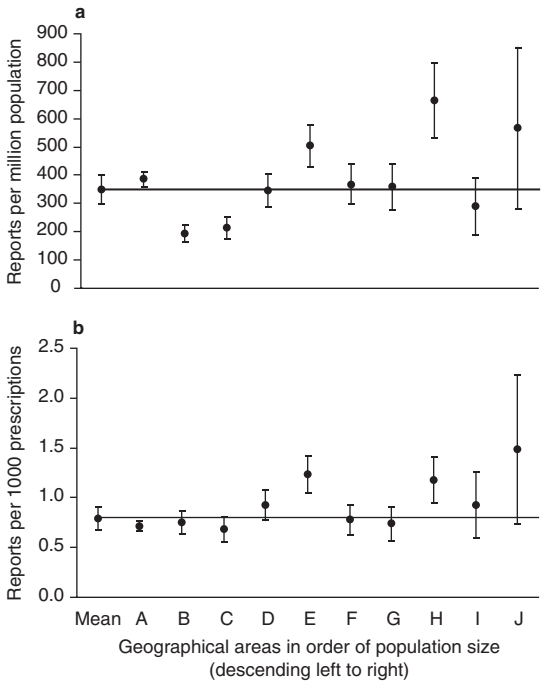

Fig. 1. Adverse drug reaction reporting rates for the 'top ten' medications from individual geographical areas (health board codes A–J) expressed as (**a**) reports per million population or (**b**) reports per 1000 prescriptions. In each case, the rate is compared with the national average for Scotland (horizontal line).

After correcting for population size, our data show a considerable 3- to 4-fold variation in the ADR reporting rate per million population between health boards and the variation for reports per 1000 prescriptions was approximately 2-fold. However, the 95% confidence intervals around the mean values for those rates overlap and show a similar degree of variation between the two measures. This simple descriptive analysis implies an association between the variations in prescribing and reporting rates between health boards, but this may have been confounded by the influence of population size on both reporting and prescribing. However, the introduction of routinely collected health board prescribing data enabled us to investigate the relationship between reporting and prescribing more closely.

There was a significant correlation between the number of prescriptions for top ten medications per million population for each health board and the number of prescriptions per 1000 population (correlation coefficient, $p = 0.66$, $p = 0.04$, respectively). From the square of this correlation coefficient, we can estimate that about 44% of the variation in reporting of ADRs that is not explained by differences in population size can be explained by variation in prescribing rates. There was no statistically significant correlation for the equivalent analysis of all prescribed items and all reports, probably reflecting the fact that the top ten medications in terms of number of ADR reports for which prescribing data were available account for about 61% of ADR reports but <2% of prescriptions.

An important potential limitation of Scottish health board data is the wide range of population sizes that are covered by the individual boards. This means that the largest health board (44% of the total population) could have had a disproportionate influence on the correlation analysis, even after taking population size into account. However, the correlation coefficient for the primary measure increased slightly and remained statistically significant after exclusion of the data from this board.

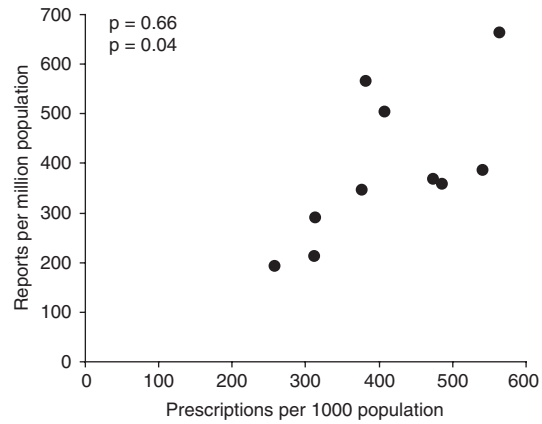

Fig. 2. Scatter plot showing the correlation between the number of adverse drug reaction reports per million of the population and the number of prescriptions per 1000 population for 'top ten' medications (2000 and 2001 combined) in each of the health boards.

Table V. Correlation between adverse drug reaction (ADR) reports per million population and prescriptions per 1000 population for individual 'top ten' medications[a] in Scotland

Drug	Year	No. of	Correlation coefficient					p-Value
	(2000/2001)	ADR reports	<0	0–0.49	0.5–0.74	0.75–0.9	>0.9	
Buproprion	Combined	1026			0.69			0.03
Rofecoxib	Combined	235			0.68			0.04
Celecoxib	Combined	102			0.55			0.10
Venlafaxine	Combined	82		0.31				0.38
Citalopram	Combined	54				0.76		0.02
Clopidogrel	Combined	47				0.78		0.008
Mirtazapine	2000	36		0.07				0.9
Donepezil	2001	31	−0.53					0.22
Reboxetine	2000	24			0.62			0.19
Leflunomide	2001	24			0.55			0.13
Alendronic acid	2001	23		0.29				0.49
Gabapentin	2000	23	−0.12					0.80
Atorvastatin	2000	23		0.28				0.58
Olanzapine	2001	22	−0.12					0.83

a In terms of the number of ADR reports to the Committee on Safety of Medicines of Scotland and excluding capecitabine and meningococcal group C vaccine.

The primary analysis suggests that, for the most commonly reported medications, regional variations in reporting rates for ADRs that are not explained by differences in population size may be related to variations in prescribing. Nearly two-thirds of ADR reports were associated with a small number of medications that accounted for <2% of all prescriptions. Among these 'top ten', the variation in national ADR reporting rates between individual medications was wide: 25- to 26-fold when expressed per million population and 130-fold for reports per 1000 prescriptions. This large variation probably relates to their individual characteristics. Some had only recently been made available for prescribing (e.g. donepezil), whereas others were large volume and, despite their intensive surveillance status, might have be considered more established (e.g. atorvastatin). Indeed, it has been previously observed that the attention span of spontaneous reporting is short and that reports about newer products predominate.[3,5-7] Publicity about ADRs can influence spontaneous reporting of these for individual drugs, and recent examples include those concerning the vaccination programme against meningococcal group C[8,9] and bupropion as an adjunct to smoking cessation.[10-12] Four of the 'top ten' medications were newer antidepressants and two were newer selective NSAIDs. There have been a number of high-profile withdrawals from the market in both classes because of serious adverse effects, and there is also evidence of channelling of agents towards those patients (e.g. the elderly) who are more likely to be vulnerable to ADRs.[13,14] Other factors relating to individual prescriptions that are likely to be important, but very difficult to quantify in epidemiological studies, are the indication, dose, duration, patient age, co-morbidities and co-prescriptions.

Other potential causes for regional variation in reporting of ADRs include the numbers and enthusiasm of reporters. Initiatives by specific groups (e.g. oncology pharmacists) can have a major influence

given that a relatively low proportion of ADRs are actually reported. The recent establishment in Scotland of both a regional reporting centre[15] and the Scottish Medicines Consortium, which provides advice to all health boards concerning the introduction of new medications,[16] should tend to reduce the regional variation observed in this study.

There are some limitations to this study. Firstly, it anticipates that exposure to a drug will follow a dispensed prescription. Although this is a well recognised surrogate, prescriptions tend to overestimate true exposure in the population, largely because of the known variability in adherence to long-term therapy. However, our primary aim was to look at the impact of primary care prescribing as a variable that influences reporting (particularly because it is amenable to influence), rather than to explore the numerous other aforementioned factors that subsequently affect the extent of exposure and risk of ADRs in individuals. Secondly, we were restricted to considering ADRs that were detected by spontaneous reporting. It is likely that these represented only a minority of the ADRs that occurred in Scotland during the study period.[3] Thirdly, there are a number of other factors that might have contributed to the marked local variation in ARD reporting rates, in addition to the population size and exposure to medications, that were not quantified. These include factors such as total reporter numbers, the presence of opinion leaders, general awareness and motivation.

While we have demonstrated the added value of considering local prescribing practices when interpreting ADR reporting, there may be further benefits from utilising primary care prescription records. Many ADRs result in significant morbidity and further specific treatment episodes within NHS Scotland. Since a record of these events is made and held by the Information and Statistics Division of NHS Scotland, there is the potential in the future to more accurately quantify the rate of ADRs by anonymously linking dispensed prescriptions to healthcare episodes (record linkage studies). The feasibility of this novel approach to pharmacovigilance has already been demonstrated within a subset of the Scottish population.[17,18]

Conclusion

Spontaneous ADR reporting in Scotland over the 2 years studied was highly concentrated on a small number of medications that were under intensive surveillance. Although there was a 3- to 4-fold variation in reporting rates from individual areas when corrected for the size of the population, the availability of primary care prescribing data showed nearly half of this local variation in reporting rates could be explained by differences in prescribing. Those areas with the highest reporting rates were also more frequently prescribing a specific subset of newer, intensively monitored, medications. This study highlights the importance of considering prescribing practice when interpreting ADR reporting data.

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