Making medicines safer

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Making medicines safer: Analysis of patient reports to the UK's Yellow Card Scheme

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Abstract

Background

No studies describing UK patient Yellow Card reports have been published since the evaluation of the first two years of direct patient reporting (2005-7), when 5,180 reports were analysed.

Research design and population

Patient Yellow Card reports submitted July-December 2015 for vaccines and other drugs were analysed. Comparisons to the initial evaluation were made of: reporting method, number of suspect drugs, proportion classed as serious. Factors affecting seriousness of reports were examined.

Results

There were 3,060 patient Yellow Card reports analysed. Vaccine reports have increased from very few in 2005-7 to 25% of reports. The proportion of reports citing one drug (94.3%) and the proportion considered serious (70.3%) increased from the 84% and 58% respectively found in 2005-7. The main method of reporting had changed from paper (61%) to internet (88.5%). Serious reports were more common in females, for vaccines in young persons, but in adults for other drugs, and included more reaction terms than non-serious reports.

Conclusions

Patient reporting, in particular to vaccines, has increased dramatically since 2005-7. Increases in the proportion of reports concerning one drug and the proportion considered serious could indicate that the usability of patient reports may have improved in comparison to early reporting.

Key words: patient reports, adverse drug reactions, side effects, patient experience, Yellow Card Scheme, pharmacovigilance

1. Introduction

It is widely acknowledged that there are considerable benefits which can result from facilitating direct patient reporting of suspected adverse drug reactions (ADRs) to regulatory authorities [1-5]. Early concerns about patient reports being incomplete seem unfounded; a small study of reports concerning the same incident concluded that the level of clinical information provided in patient reports was similar to that of healthcare professionals (HCPs) [6]. Patient reports complement reports submitted by HCPs, as they often contain information which provides explicit detail of the effects of ADRs on the patient's life, family and/or carers. These additional details create a richer narrative and help to form a more comprehensive picture of the individual's experiences of ADRs [7,8].

A review of direct patient ADR reporting in 11 countries conducted in 2012 found that most had three methods for patients to report ADRs; paper, electronic or telephone. While all recognised the importance of facilitating the public in reporting ADRs and the scientific value of this data, only the UK and The Netherlands had actively evaluated their patient reporting schemes [9]. A later survey, reported in 2015, found that 44 countries had systems for direct patient reporting, 31 via an on-line form [10]. There were variations found in the content of the reporting forms, with the number of required fields ranging from 6 to 50. This review found that patient reports represented only 9% of all submitted reports. This was confirmed by a more recent systematic review which concluded that despite the availability of patient reporting, in practice it was relatively rare in most countries [5]. Within the EU, legislation requiring patient reporting systems came into force in 2010, following which the proportion of patient reports increased. During the period from July 2014 to July 2015, approximately 15% of all reports across the EU were submitted by patients to the Eudravigilance database, with the Netherlands, UK, Germany, France and Italy accounting for 75% of all patient reports submitted [11]. A SCOPE (Strengthening Collaborations in Operating Pharmacovigilance in Europe) work package provided advice and support on ensuring best practice in ADR reporting, including guidance on raising awareness of patient reporting and comparing patient and health professional reports [12]. Since 2016, annual EU-wide social campaigns led by the Medicines and Healthcare Regulatory Agency (MHRA), as well as national campaigns [13-16] have sought to increase public awareness about reporting side effects. Moreover, it is now mandatory for patient information leaflets to include a statement about reporting suspected ADRs, which should also contribute to increased awareness of reporting among patients.

In the UK, direct patient reporting has increased considerably since it was introduced by the MHRA in 2005. Over the first two years of the scheme, patients contributed 5,180 reports, with the proportion of reports considered serious being similar between patients and health professionals at 58% [17]. By 2015, the number of patient reports submitted had reached an annual total of 5,459, making up 14% of all direct reports, and they had contributed towards 15 signals being detected, including six where a patient report directly stimulated regulatory action [18]. Patient reporting has continued to rise, with the proportion of patient reports in 2017 constituting 26% of reports from non-industry sources [19]. In 2018, the proportion rose to 28%, with the highest number of Yellow Card reports ever received since the scheme's launch with 8,272 reports received (M. Jajada, personal communication). Efforts by the MHRA and its five Yellow Card Centres via engagement with patient associations and organisations, plus Patient and Public Stakeholder Engagement outreach work are likely to have contributed to this increase.

However, since the initial evaluation of the UK's patient reporting system in 2011 [3], no further research studies describing patient reports submitted to the MHRA have been published. At that time nervous system disorders were the most common reported ADR type, with 16% of reports containing more than one drug. Patients reported a mean of three reactions per report. Now patient reporting has become routine and established in the UK, the profile of patient reporting in the initial analysis may have changed. Moreover, no studies have examined patient reports in detail, the purpose of the early evaluation being a high level comparison between patient and health professional reports.

We therefore undertook a study to analyse a large sample of patient Yellow Card reports. This included analysing the written content to explore patients' ADR experiences as reported on Yellow Cards. In addition, a descriptive analysis of the patient reports was also conducted, which we report here. The objectives of this study were: (i) to describe all patient reports submitted to the MHRA over a six-month period in terms of reporter characteristics, drugs, reactions and outcomes; (ii) to explore factors associated with reports classed by the MHRA as serious; and (iii) to compare selected parameters to the analysis of reports from the first two years [3].

2. Patients and methods

The study received favourable ethical approval from the Independent Scientific Advisory Committee for MHRA database research (ISAC Ref: AYC042). All patient Yellow Card reports received by the MHRA during a six-month period from July to December 2015 were analysed. MHRA staff provided the anonymous data in a series of Excel spreadsheets in a password protected form. Each individual report had a code number which was used to match the data from the separate Excel spreadsheets, enabling a single dataset to be derived which contained: reporter code number, type of reporter (parent, patient, carer), reporting method, age and gender of person experiencing ADR, suspect drugs, number of reaction terms, whether or not categorised by the MHRA as serious and outcomes (life-threatening, hospitalised, disability/incapacity, congenital abnormality, death). The analysis of the free text responses to all open questions on Yellow Cards is reported separately.

All individual drugs in each report were classified using British National Formulary (BNF) number 69 (March 2015) and the total number of different drugs and different products were calculated for each report. Due to the differing nature of vaccines, as biological substances which are extensively used across all age groups, reports concerning vaccines were separated out from reports concerning other drugs and comparisons made between these two groups of reports. Reports to both vaccine and other drugs were examined for potential factors associated with reports being categorised as serious by the MHRA. Differences between sub-groups were made using Chi-squared tests and independent t-tests as appropriate, with a p value of 0.05 accepted as indicating statistically significant differences.

Findings were also compared to those reported in the evaluation of the first two years of patient Yellow Card reporting in terms of: reporting method, gender, proportion considered serious, number of suspect drugs and common therapeutic groups [3].

3. **Results**

A total of 3,060 patient reports were received by the MHRA during the six-month period, of which 776 (25.0%) concerned vaccines.

3.1 Reporting method

The large majority of all reporters used the internet 2708 (88.5%), with only 98 (3.2%) using the telephone, and 247 (8.1%) using paper forms. The remaining seven reports were received through other methods. There were fewer reports concerning people aged 65 or over submitted via the internet (454/590; 76.9%) than for younger people (2206/2322; 95.0%).

3.2 Reporter type

Most patients self-reported suspected ADRs (2,457; 80.3%), 15.9% (n=487) reports were submitted by parents and the remaining 3.8% (n=116) by carers, although there were differences for reports concerning vaccines compared to other drugs. For vaccines, 51.2% of reports (n=397) were submitted by parents and only 46.5% (n=364) by the patients themselves, whereas for other drugs, the majority of reports were submitted by the person experiencing the reaction (2096; 91.8%).

3.3 Gender and age

There was a higher proportion of reports concerning females for both vaccines (475; 61.2%) and other drugs (1524; 66.7%). Fewer vaccine reports (18; 2.3%) had age missing than reports for other drugs (130; 5.7%). Among the 10 to 18 age group, 79% of the reports involving vaccines were submitted by parents, in contrast to other drugs, where parents were responsible for fewer reports (64%). Based on the data, the youngest patients who self-reported were 12 years of age and the oldest were 89.

The distribution of reported ADRs by age differed, with over half the vaccine reports concerning infants, children and young people under 18 years of age in contrast to other drugs, where the majority of reports concerned adults aged 19 to 64 (Table 1).

The distribution of gender across different age groups was similar for both vaccines and other drugs, with reports concerning females predominating among those aged 10 to 64, whereas there were more reports concerning males in older age groups. For vaccines, the mean age of reports was similar for males (27.0 years) and females (28.9 years), whereas for other drugs, the mean age of males experiencing an ADR (51.8 ± 21.1 years) was significantly higher than for females (44.6 ± 18.0).

3.4 Number and type of drugs

The total number of drugs cited in the 3,060 reports was 3,434; an average of 1.12 per report. The large majority of reporters cited only one suspect product for both vaccines (719; 92.7%) and other drugs (2,082; 91.2%). For vaccines, 37 (4.8%) cited two, 12 (1.5%) three and 8 (1.0%) four, while for other drugs 148 (6.5%) cited two, 34 (1.5%) three and 20 (0.9%) four or more products. The maximum number of products cited for vaccine reports was four whereas for other drugs it was seven. A proportion of reports contained multiple strengths of the same drug, therefore overall the range of different drugs cited was 1 to 6 and the proportion of reports containing only one drug was 2,885 (94.3%).

After vaccines, the most common therapeutic areas were central nervous system (18.0%) and anti-infective agents (13.3%). Proportionately more females than males reported central nervous system drugs, while more males reported cardiovascular drugs. Table 2 shows the frequency of the distribution of reports between therapeutic areas by gender, along with the most common drug group in each category. Both young people and adults submitted reports across all therapeutic areas. However, in both younger (18 or below) and older people (65 or above), the most commonly reported therapeutic area (excluding vaccines) was central nervous system, while in adults aged 18 to 64 it was cardiovascular drugs. There were 58 reports concerning drugs from more than one BNF chapter (35 female and 23 male), across all age groups.

3.5 Number of reaction terms

The number of reaction terms reported was similar between vaccines and other drugs, the overall mean being 3.91. (Table 3). Overall 754 (24.6%) of all reports contained only one reaction term, but this proportion was slightly lower for reports concerning vaccines. There were more reaction terms reported for females than for males for both vaccines and other drugs. For vaccines, the number of reaction terms reported varied considerably with age, being highest in young persons (18 or under) and lowest in those aged 75 or over. In contrast the number of terms did not vary significantly with age for other drugs (Table 3).

The mean number of reaction terms per report was highest for endocrine drugs (4.50 ± 3.92; n=183), followed by centrally-acting drugs (4.30 ± 4.56; n=550). The lowest mean number of reaction terms reported concerned over-the-counter (2.81 ± 2.05; n=72) and herbal products (2.67 ± 1.46; n=18), together with BNF Chapter 12 (ear, nose and oropharynx) (2.78 ± 3.65; n=32).

3.6 Seriousness and outcomes
Outcomes were similar between vaccines and other drugs, with the exception of life-threatening reactions, which were less common for vaccines (Table 4). The proportion of reports categorised as serious by the MHRA was similar for vaccines (68.4%) and other drugs (71.0%). The therapeutic group which resulted in the highest proportion of life-threatening events, also resulting in hospitalisation was musculo-skeletal (11 and 17 out of 118 total events respectively), whereas endocrine drugs resulted in the highest proportion of events resulting in disability or incapacity (32/183 events).

3.7 Factors affecting seriousness of reports

Gender: For general drugs, significantly more females reported serious ADRs (1,115; 73.2%) than males (506; 66.6%), whereas for vaccines, the difference was much less marked – 330 (69.5%) in females compared to 201 (66.8%) in males.

Age: The proportion of reactions to general drugs reported as serious occurred more frequently in adults (72.9%) than in those aged below 18 (66.4%). However for vaccines this was reversed, with the proportion of reports considered serious being higher in infants, children and young people (75.0%) than in adults (61.9%).

Number of drugs: Seriousness was not related to the number of drugs cited either for vaccines or other drugs.

Type of drug: Reports involving drugs from BNF Chapters 9 (nutrition and blood), 12 (Ear nose and oropharynx), 13 (Skin) plus herbal and over the counter products were less frequently classed as serious, while reports involving drugs from Chapters 6 (Endocrine) and 8 (Malignant disease and immunosuppression) included the highest proportions of serious reports.

Number of reaction terms: Among general drugs, significantly more reaction terms were selected for reports categorised as serious by the MHRA: 4.44 +/- 4.08 (n=1621) compared to non-serious reports, which included only 2.4 +/- 1.88 (n=663) reaction terms (p<0.001, t-test). There was a similar finding for vaccine reports: the number of terms in serious reports was 4.69 +/- 3.68 (n=528) compared to 2.70 +/- 2.11 (n=248) in non-serious reports (p<0.001, t-test).

3.8 Comparison to previous data

The evaluation of the first 5,180 patient reports submitted to the Yellow Card Scheme found that 63% were in females, and the main method of reporting then was paper (61%), with only 13% of reports being submitted via the internet [3]. The proportion considered serious by the MHRA was 58%, 16% contained more than one suspected drug and 22% reported over five reactions. The commonest therapeutic groups were central nervous system, cardiovascular and anti-infective drugs, which included vaccines (Figure 1).

In 2015, the proportion of reports concerning females was similar to 2005-7 [3], however there was a very large growth in internet reporting, from 13% to 88%. The proportion of reports involving more than one drug in 2015 (8%) was much lower than in 2005-7, while the proportion of serious reports was higher (70.3%). The proportions reporting life-threatening events, hospitalisations and deaths were all lower in 2015 compared to 2005-7. However, the proportion who cited more than five reactions was similar at 21%. The commonest therapeutic groups cited were also similar, with the exception of vaccines, which were much less frequently reported by patients in 2005-7, yet represented the largest group in 2015.

4. Discussion

This in-depth analysis of patient Yellow Card reports to the MHRA shows that since 2005, reporting has increased considerably for vaccines, proportionately more than the increase in patient reporting in general. It also found that the proportion of reports citing only one drug has increased, which, together with the increase in the proportion considered serious, suggests that value of patient reports may have improved, since the former should increase the ease with which attribution can be assessed and the latter means that the reports concern potentially important effects. The method of reporting has changed dramatically from predominantly paper to internet, in line with other studies showing increased internet use [20] and, although older people are still less likely to use this method of reporting, the difference was much less than in 2005-7 [3]. MHRA data show that 89% of patient reports were submitted electronically in 2017 [21], however this is also influenced by the launch of a mobile application, both of which reporting methods are encouraged by the MHRA.

Vaccines barely featured in early reporting [17], but several were among the top 20 most commonly reported drugs within the Eudravigilance system between 2009 and mid-2015 [11]. The most likely

contributors to this large increase are the introduction of new vaccines into the NHS routine vaccination programme, the increased availability of private influenza vaccination through community pharmacies and major promotion campaigns, all of which result in greater use of vaccines. The high proportion of vaccine reports submitted in the second half of 2015 enabled a comparison to be made with reports for other drugs and some key differences were found. Vaccine reports more frequently concerned infants and young people and consequently were reported more often by parents. Previous research suggested that parents were unaware of the procedures in place for postmarketing surveillance of vaccines and that greater promotion of patient reporting was needed [21]. The findings suggest that increased promotion may indeed have created a greater awareness of reporting. As well as more frequent reports, the number of reaction terms was higher in vaccine reports concerning infants and young people, in comparison to other drugs and reports concerning vaccines in older people. Reasons for this are unknown, thus may be worthy of further research.

The highest proportion of reports overall was found in patients aged 19 – 44 years. This may appear surprising in view of the fact that medicines use increases with age [23] and older people are at increased risk of ADRs [24]. One possible reason may be that people in this age group have been found to perceive themselves as more burdened by their medicines than older people [25], while older people have been found to be more satisfied with health care than younger people [26]. A further factor may be the ease of reporting via the internet, which may have contributed to proportionately lower reporting by older people.

As has been found previously [3,11] females were the subject of more reports than males. Such differences are not surprising, since women tend to use more drugs in general than men [22], in England mostly younger women [23]. However, the study also found differences in the drugs which were cited between the genders, particularly for endocrine, anti-infective and cardiovascular medicines. Differences in drugs and reported symptoms between the sexes have previously been shown in large-scale studies [27, 28]. In addition, females were more likely to report serious reactions and to include more reaction terms in reports than males.

The study also found that females were likely to report serious reactions and to include more reaction terms in reports. Overall, the mean number of reaction terms per report (3.91) was slightly higher than that found in a cross-European study (3.33) [11], with more reaction terms being cited in serious reports.

The therapeutic groups cited in patient reports to an extent reflected prescribing data with the highest proportion of reports after vaccines involving centrally acting drugs, anti-infectives and cardiovascular drugs. Cardiovascular (particularly lipid-lowering and antihypertensive drugs) and centrally-acting drugs (particularly antidepressants) are those most commonly prescribed in the community [29], therefore the high proportion of reports is not unexpected. Endocrine drugs, the third most frequently prescribed drug group, included the highest proportion of reports resulting in disability or incapacity and also the highest proportion considered serious. Drugs for musculo-skeletal and joint diseases, although much less frequently prescribed, had the highest proportion of reports resulting in hospitalisation and life-threatening events. Again, this is unsurprising in view of the known toxicity of many drugs within this category [30]. Research has shown that antibacterials were prescribed at a median rate of 626 prescriptions/1000 patients in 2015, with penicillins

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accounting for 50% of all prescriptions, followed by macrolides (13%), tetracyclines (12%) and trimethoprim (11%) [31]. Thus patient reports of suspected ADRs are also in line with these prescribing patterns.

Although the proportion of reports considered serious was much higher than in the first two years of patient reporting, the proportion considered life-threatening, causing hospitalisation and death were all lower [17]. One potential reason for this is that reports submitted during 2005-7 included historical reports of reactions with very serious consequences which patients had previously been unable to report themselves. Thus the median time to report during the first two years of reporting was 104 days [17], in contrast to 32 days found in more recent Eudravgilance data [11].

The study was limited in terms of the period and thus quantity of reports available and also relates to several years ago. We were inevitably reliant on the accuracy of the responses completed by the patient reporters in our analysis. The period selected included the time frame for national vaccination campaigns for influenza and pneumococcus, which would have affected the number of vaccine reports. We did not set out to study the impact of patient reports on signal generation or to make comparisons with reports submitted by health professionals. However, the MHRA confirms that patient reports are generating more signals.

5. Conclusions

Direct patient reporting via the Yellow Card Scheme is increasingly providing a significant proportion of pharmacovigilance data. The majority of direct patient reports of suspected ADRs to the MHRA are submitted electronically, regardless of age and include a high proportion concerning vaccines. The latter should provide re-assurance that patients and carers are more aware of reporting systems. Most reports cite only one drug and a small number of reaction terms and 70% are considered serious. We believe this indicates the increasingly important role which patient reporting plays in pharmacovigilance, since it suggests that the potential usability of patient reports has improved in comparison to the first two years of patient reporting, although their value in generating signals also depends on their clinical quality.

Author contributions

Conception and design (all authors), analysis and interpretation of the data (J Krska, R Rodgers and B O' Donovan), drafting and revising of the paper (J Krska, A Cox and B O' Donovan), revising, final approval (J Krska, A Cox and B O' Donovan); and all authors agreed to be accountable for all aspects of the work.

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** Initial evaluation of YC reports from the first two years of the YCS

* Analysis of patient reports to the Eudravigilance database which compares patient reports with those from healthcare professionals

* Prescribing data for England 2007-2017 which provides context for research findings and suggests patient reports reflect prescribing patterns

*Antibiotic prescribing data in England 2013-2015 which provides context for research findings and suggests patient reports reflect antibiotic prescribing behaviours