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Actions in response to drug safety signals arising from a spontaneous reporting system: Retrospective study in The Netherlands

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Abstract.

BACKGROUND: There is limited information on actions taken in response to drug safety signals originating from a spontaneous reporting system (SRS) in pharmacovigilance. In The Netherlands the Pharmacovigilance Centre Lareb is an independent organization that works in close collaboration with the Dutch regulatory agency, the Medicines Evaluation Board (MEB).

OBJECTIVE: The objective of this study is to gain insight in steps undertaken on signals originating from the SRS and disseminated by Lareb from 2008–2012.

METHOD: For all signals the recommendations of Lareb and the following steps proposed by the MEB were analyzed. Secondary outcomes were prioritization of the signal, the year of dissemination and if Lareb published (inter)nationally about the signal. Pearson's Chi-square (X^2) and Mantel-Haenszel statistics were used for statistical analysis.

RESULTS: Of all signals disseminated by Lareb from 2008–2012, 90,7% resulted in an action: in 87% a regulatory action and in 36% an (inter)national publication. Generally, Lareb's recommendations correspond to steps undertaken by the MEB.

CONCLUSION: This study found influence of signal prioritization on Lareb's recommendations but not on the steps undertaken by the MEB. Trends over time were only seen for steps undertaken by the MEB. These differences are most probably due to responsibilities of the different EU member states of various drugs.

Keywords: Adverse drug reactions (ADRs), pharmacovigilance, signals, post marketing drug safety

1. Introduction

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem is also known as 'pharmacovigilance' [1]. Due to a selected population and limitations in study period during pre-approval clinical trials, the safety

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profile of a drug is only partly known after marketing authorization, making drug safety monitoring an ongoing process [2].

Pharmacovigilance centers, maintaining the national Spontaneous Reporting System (SRS), aim the timely detection of drug safety signals. These signals include unknown adverse drug reactions (ADRs) as well as information about new aspects to known drug-ADR associations [3, 4]. Identifying signals is a selective process based on the apparent strength of the evidence and the potential importance of the association. In practice, a signal is something that, if found to be drug related, would be considered clinically important and might have impact on patient management or the balance of benefits and risks [5].

1.1. National pharmacovigilance centre

In The Netherlands, the SRS is maintained by the Netherlands Pharmacovigilance Centre Lareb. Signal detection is carried out mainly by means of a case-by-case analysis. Each incoming ADR report undergoes an individual systematic review. All ADR reports with potential signal value are reviewed by trained assessors during a weekly meeting. Potential signals undergo a more detailed analysis. Information taken into account during such an analysis is: strength of the cases, possible mechanism, information available in literature, the potential health impact and the disproportionality of the drug-ADR association by means of the reporting odds ratio (ROR) in the database of Lareb and the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC). In addition to the case-by-case signal detection approach, Lareb carries out a screening for signals that are disproportionally present in the database.

1.2. Signal dissemination by Lareb

The Dutch Pharmacovigilance Centre Lareb is an independent foundation funded by the Ministry of Health [6]. Lareb works in close collaboration with the Dutch Medicine Evaluation Board (MEB) and until recently has informed the MEB periodically about the most relevant drug safety concerns in a so-called ‘quarterly-report’. Since 2015, reports on safety concerns are sent to the MEB on a continuous basis. Top priority safety signals that cannot wait for publication in a quarterly report were and still are sent to the MEB immediately by means of a letter. Associations described in the quarterly reports may present drug safety concerns e.g. new ADRs, interactions, but also overviews of ADRs of drugs that were marketed recently in the Netherlands. Sometimes an update of an older signal which still warrants attention is given. Since the goal of this quarterly-report is to give an early warning to the authorities, the ‘signals’ described by nature have a premature character [7]. Besides a description of the scientific information about the drug-ADR association, Lareb gives a recommendation of what action(s) to take in response to the signals e.g. “ADR should be mentioned in the Summary of Product Characteristics (SmPC)” or “The signal should be further investigated”.

In addition to informing the regulatory authority, Lareb informs the pharmacovigilance community, healthcare professionals and patients about some signals through (inter)national newsletters and publications in (inter)national journals.

1.3. Handling signals by the MEB

The MEB assesses and guards the efficacy, safety and quality of both human and veterinary medical products on the Dutch market. It shares responsibility for authorizing medicinal products throughout the European Union (EU) and has autonomous powers to take decisions on the authorization and availability of these medicinal products [8].

All signals reported by Lareb are discussed during a MEB-meeting, mostly resulting in a regulatory action. Lareb's recommendations are taken into account by the MEB but are not decisive. Other information and aspects than those mentioned in the report of Lareb are taken into account. There are multiple levels of regulatory actions, some examples are: "The signal will be evaluated in the next PSUR", "The signal will be send to the Reference Member state (RMS) and/or the Rapporteur", "The Marketing Authorization Holder is asked for more information" [9]. A previous overview showed that proposed actions on signals reported by Lareb were mostly restricted to forwarding the information to the RMS and/or Rapporteur, evaluation of the Periodic Safety Update Report (PSUR) or changes of the SmPC [10].

1.4. The role of the European Union

In Europe, the role of the EU is becoming increasingly important in pharmacovigilance. Since the introduction of the new pharmacovigilance legislation in 2012, several tools have been implemented to enhance the quality of postmarketing safety of approved medicinal products in the EU [11]. An important change is the introduction of the Pharmacovigilance Risk Assessment Committee (PRAC) [12]. The PRAC is responsible for assessing and monitoring safety issues for human medicines. It consists of scientific experts of each European Member State. In addition, six independent scientific experts are appointed by the European Commission to represent healthcare professionals and patient organizations [13]. Pacurariu et al. described the signals as brought to the PRAC during the first 18 months of its operation and the ensuring regulatory actions. Of all 125 signals, 51 recommended a SmPC update, 33 routine pharmacovigilance and 9 to start a referral procedure to resolve the issue. For 7 signals a Dear Healthcare Professional Communication was recommended and for 7 a Risk Management Plan. It is possible that there is more than one recommendation per signal [14].

Due to the changes on European level, also the possibilities for actions taken by the MEB on reports of Lareb have been changed.

1.5. Signal disseminated, what's next?

There is limited information on actions taken in response to signals originating from a SRS in pharmacovigilance. Signals with top priority may need more fundamental regulatory actions compared to signals with lower priority. This applies to recommendations/actions of Lareb and the MEB, but also for (inter)national publications of Lareb. At the moment it is however unclear if there is a relation between signals prioritization – based on their signal strength and potential health impact – and its actions. Further it is unclear if actions differ over time, for example by the increasing role of the European Medicines Agency (EMA).

The aim of this study is to gain insight in steps undertaken on signals originating from the SRS and disseminated by Lareb from 2008–2012 to the MEB and/or (inter)national journals. In addition, the influence of signal prioritization on these recommendations/actions and trends over time are explored.

2. Methods

A retrospective review of drug safety signals disseminated by Lareb was performed to gain insight in steps undertaken on these signals. All signals that were disseminated by Lareb from 2008–2012 were taken into account.

2.1. Actions in response to the signals

For all signals the recommendations of Lareb as written in the quarterly-report at the end of each signal and the following steps proposed by the MEB based on the MEB-meeting minutes were analyzed. As a secondary outcome, it was checked if Lareb published (inter)nationally about the signal, the year the signal was disseminated, and the prioritization of the signals based on the Regulatory Pharmacovigilance Prioritization System (RPPS) [15] were analyzed. Comparisons were made between signal prioritization and: recommendations of Lareb, following steps proposed by the MEB and publication about the signal by Lareb.

2.2. Signal prioritization using RPPS

A RPPS, described by Seabroke et al. was used in order to explore the influence of signal prioritization on the actions taken on the signals [15]. The RPPS has 16 inputs considered to be most important for prioritizing pharmacovigilance issues. Inputs are shown in Table 1. The overall score is calculated from the sum of all points from each input. The RPPS prioritizes signals in one of three categories: A: ≥ 14 points meaning top priority, category B: 6–13 points is increased priority and category C: 0–5 points meaning standard priority.

2.3. Statistical analysis

Pearson's Chi-square (X^2) and Fisher's exact tests were used for statistical analysis. Mantel-Haenszel statistics was used to explore possible trends for actions over the years. Significance was based on a two-sided test; $P < 0.05$.

Table 1
Inputs of RPPS

Category	Input	Number of points
Public health implications	Drug/vaccine exposure	3
	Frequency of ADR	2
	Health consequences	4
	Spontaneous case reports	1
Regulatory obligations	Ministerial/public health authority concern	1
	Recent parliamentary questions	1
	European obligations	3
	Marketing Authorization Holder application	2
Strength of evidence	Disproportionality measure/risk estimate	2
	Data sources	4
	Evidence from RCT or meta-analysis	4
	Biological plausibility	2
Public perceptions	Media attention	3
	Factors likely to cause public anxiety	4
	Public misperceptions	1
	Other public concerns	3

3. Results

From 2008 to 2012 Lareb disseminated a total of 97 drug safety signals. A list with specific drug-ADR associations relating to the signals is available online in Supplementary data 1.

3.1. Prioritization of signals

Of all signals, 14 (14.4%) were prioritized as top priority, 63 (64.9%) as increased priority and 20 (20.6%) as standard priority. Examples of signals with top priority: “Ibuprofen and Stevens Johnson Syndrome/Toxic Epidermal Necrolysis”, “Tocilizumab and necrotising fasciitis” and “Medication for Attention-Deficit Hyperactivity Disorder (ADHD) and suicidal tendency (suicidal ideation and suicidal behaviour)”. Examples of signals with increased priority: “Valproic acid and gingival disorders” and “ACE-inhibitors and nightmares or abnormal dreaming”. Examples of signals with standard priority: “Bisphosphonates and depressive reactions” and “Methylphenidate and epistaxis”.

3.2. Recommendations of Lareb and steps undertaken by MEB

An overview of the recommendations of Lareb and following steps proposed by the MEB for the included signals is shown in Table 2. In 87% of the signals, a following step is proposed by the MEB, recommendation “Lareb is asked to review the ADR (for class effect)” not included. For only 13% no further steps were taken.

For most signals the MEB proposed another action compared to Lareb’s recommendation. In most cases MEB is not primarily responsible for the drugs concerned in these signals. Most of these drugs are registered via European procedures for which either EMA or another EU member state is responsible. Therefore the MEB only proposed “the signals will be send to the RMS and/or Rapporteur”. For

Table 2
Overview of recommendation of Lareb and actions proposed by the MEB

Recommendation of Lareb	Proposed actions MEB*							
	Signal will be evaluated in next PSUR review	Signal will be send to the RMS and/or rapporteur	The MAH must put the ADR in the SmPC	No further action taken	The MAH is asked for more information	The signal is send to the Dutch Health Inspectorate [^]	The signal will be discussed in the PhVWP	Lareb is asked to review the ADR (for a class effect)
ADR should be mentioned in the SmPC	13	26	16	2	10	0	2	3
(Possible) new signal	5	9	2	3	2	1	2	4
Attention to this association in PSUR may be warranted	1	2	0	0	0	0	0	2
The signal should be further investigated/more information is needed	5	6	0	7	0	0	3	1
Signal that should be important for the Dutch Health Inspectorate	0	0	0	1	0	0	0	0

*More than one action per signal was possible. [^]As a consequence of the new pharmacovigilance legislation, the PhVWP (Pharmacovigilance Working Party) is replaced by the PRAC (Pharmacovigilance Risk Assessment Committee) which is responsible for assessing and monitoring safety issues for human drugs at a European level.

example the association “Adalimumab and pustular psoriasis” or “Tocilizumab or necrotising fasciitis”. For some other signals, for example for the associations “Triamcinolone acetonide injection and postmenopausal haemorrhage”, the MEB proposed the action that “the signal will be evaluated in the next PSUR review”.

3.3. Recommendations Lareb and steps undertaken by MEB versus prioritization and trends over time

Comparing Lareb’s recommendation with signal prioritization, Lareb’s recommendation “ADR should be mentioned in the SmPC” was more often recommended for signals with top and increased priority than for standard priority ($p = 0.03$). No trends were seen for Lareb’s recommendations over time.

No differences were found comparing prioritization with the steps undertaken by the MEB. Statistical analysis showed a trend over time for the action “The Marketing Authorisation Holder (MAH) must put the ADR in the SmPC” ($p = 0.001$). Over time, this action was less often proposed. The same applies to the action “The signal will be discussed in the Pharmacovigilance Working Party (PhVWP)” ($p = 0.03$). Over time, the action “The signals will be sent to the RMS or Rapporteur” was more often proposed.

3.4. Publications by Lareb

Lareb published 39 papers about 35 of the 97 signals; 25 national and 15 international publications [16]. Lareb published about 3 (21.4%) signals with top priority, 26 (41.3%) signals with increased priority and 4 (20%) signals with standard priority.

No differences were found when the publications were compared with the signal prioritization or year of dissemination (respectively $p = 0.38$ and $p = 0.68$).

From the 13 signals for which the MEB suggested “no further action”, Lareb published on four of these signals [17–22]. For the association SSRIs and aggression Lareb recently published an update for this signal in the quarterly-report. After this updated signal the MEB forwarded the signal to the EMA. The PRAC discussed the information on the cases reported and decided that further review of the signal was warranted, taking into consideration spontaneous sources and clinical trial data, as well as data from scientific literature [23].

An example of a national publication of a signals with top priority is the association of “SSRIs and hypoglycemia in patients with diabetes mellitus” in the Dutch drug bulletin [24]. Hypoglycemia is not described as ADR in the SmPC of SSRIs. The SmPC warns for possible deregulation of glycemic control. Lareb received 12 reports of hypoglycemia associated with the use of SSRIs. This association is well described in literature. By this national publication Lareb wanted to inform Dutch healthcare professionals. “Oral terbinafine and hearing disorders” is a signal with increased priority which was published internationally [25]. Lareb received 6 reports of hearing disorders with the use of oral terbinafine. In two cases a positive dechallenge was reported. This association is not described in literature and there is no known mechanism. The association is however disproportionally present in the Lareb database. Since hearing disorders with the use of oral terbinafine is not described before in literature, this association was internationally published.

4. Discussion

This study showed that 87% of the signals disseminated by the Dutch pharmacovigilance centre resulted in a following step by the Dutch regulatory authority (MEB). It was assumed that signals with

higher prioritization would result in different recommendations and following steps undertaken by the MEB. This was shown for Lareb's recommendation "ADR should be mentioned in the SmPC". This recommendation was more often given for signals with top and increased priority than for standard priority. This result was not shown for following steps of the MEB. Also, Lareb's recommendation "the ADR should be mentioned in the SmPC" did not always correspond the following step of the MEB. These two findings may be explained by responsibilities of the different EU member states in the marketing authorization of various drugs. As shown in this overview, regulatory actions are various. For most signals for which the MEB proposed another step compared to Lareb's recommendation, the EMA or another EU member state is primarily responsible for the drugs concerned in these signals. For drugs registered via the national route the MEB will actively request the MAH to submit a so called 'adaption, to include the signal in the SmPC. The same applies when the Netherlands is acting as RMS in an EU procedure. If the Netherlands's role is Concerned Member State (CMS), the RMS(s) or Rapporteur will be informed about the signal.

The trend over time for the conclusion of the MEB "The MAH must put the ADR in the SmPC", which was less often proposed over time and "The signals will be send to the RMS or Rapporteur" which was more often proposed is also a reflection of the increasing role of the EU in pharmacovigilance.

Besides informing the regulatory agency about new drug safety signals it is also important to inform healthcare professionals, patients and professionals working in pharmacovigilance. The signals published in the quarterly-reports are freely accessible at the Lareb website. However, we are aware of the fact that this information doesn't always reach healthcare professionals and patients. As shown in this overview, Lareb also reported about signals where the MAH proposed no follow-up steps. By (inter)national publications we try to raise awareness about new drug safety signals.

Informing about ADRs may also stimulate healthcare professionals and patients to report these (or other ADRs).

4.1. Strengths and limitations

A strength of this study is that we included drug safety signals disseminated by Lareb over a 5-year period. This would be a good reflection of drug safety signals disseminated over time. RPPS was used for signal prioritization. At the moment there is no gold standard for signal prioritization in pharmacovigilance. Lareb has an operating tool for signal selection which scores for signal strength and health impact. Testing of this tool showed low validity [26], which made us search for another method. The RPPS was tested in a pilot and implemented in the UK pharmacovigilance centre. Overall, the results of both the pilot study and the post-implementation show that the RPPS provides a consistent, systematic approach to issue prioritization that removes some of the subjectivity of reliance on the judgment of members of a meeting [15].

At Lareb, signals published in quarterly-reports are drafted by several pharmacovigilance assessors and a chief editor. Over the years, there were several instructions of how these assessors should formulate a recommendation. Since 2011 there is a more structural standard operating procedure which results in a more uniform recommendation. Differences in recommendation formulation may however influence the results of this study.

4.2. Vision for the future

For the future, Lareb and the MEB will continue their exchange of drug safety information. Efforts will be made to improve the process. We want to focus on a more continuously information flow. In this case, signals are not disseminated only four times per year but in a more continuous manner.

Another improvement that has already been established is sharing information about a possible safety signal in an earlier stage between Lareb and the MEB. In this way, all information available at Lareb and the MEB about an association can be taken into account.

Because we believe that communication is an important aspect of pharmacovigilance, Lareb makes efforts for improvements. Recently Lareb introduced an (inter)national newsletter which is sent by e-mail to healthcare professionals and patients. In this newsletter they are informed about the newest disseminated signals and other drug safety news. This newsletter is also published on the website where it is freely accessible.

5. Conclusion

This study gives an overview of actions taken on signals originating from a SRS. Of all signals disseminated by Lareb from 2008–2012, 90,7% resulted in an action: in 87% a regulatory action and in 36% (inter)national publication.

Generally, Lareb's recommendations correspond to steps undertaken by the MEB. This study found influence of signal prioritization on Lareb's recommendations but not on the steps undertaken by the MEB. Trends over time were only seen for steps undertaken by the MEB. These differences are most probably due to responsibilities of the different EU member states of various drugs.

Conflict of interest

The authors have no conflict of interest.

Competing interests/funding

None to declare.

Supplementary material

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JRS-160724>.

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