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Prescription-Event Monitoring
Developments in Signal Detection

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Abstract

Prescription-event monitoring (PEM) is a non-interventional intensive method for post-marketing drug safety monitoring of newly licensed medicines. PEM studies are cohort studies where exposure is obtained from a centralised service and outcomes from simple questionnaires completed by general practitioners. Follow-up forms are sent for selected events.

Because PEM captures all events and not only the suspected adverse drug reactions, PEM cohorts potentially differ in respect to the distribution of number of events per person depending on the nature of the drug under study. This variance can be related either with the condition for which the drug is prescribed (e.g. a condition causing high morbidity will have, in average, a higher number of events per person compared with a condition with lower morbidity) or with the drug effect itself.

This paper describes an exploratory investigation of the distortion caused by product-related variations of the number of events to the interpretation of the proportional reporting ratio (PRR) values ("the higher the PRR, the greater the strength of the signal") computed using drug-cohort data.

We studied this effect by assessing the agreement between the PRR based on events (event of interest vs all other events) and PRR based on cases (cases with the event of interest vs cases with any other events). PRR were calculated for all combinations reported to ten selected drugs against a comparator of 81 other drugs. Three of the ten drugs had a cohort with an apparent higher proportion of patients with lower number of events. The PRRs based on events were systematically higher than the PRR based on cases for the combinations reported to these three drugs. Additionally, when applying the threshold criteria for signal screening (n ≥3, PRR ≥1.5 and Chi-squared ≥4), the binary agreement was generally high but apparently lower for these three drugs.

In conclusion, the distribution of events per patient in drug cohorts shall be examined when comparing the 'strength of the signals' across drugs using PRR values. Further research will be required to address the sensitivity and specificity of the two ways of calculating PRR using data derived from drug cohorts.

"*Disproportionality techniques developed to review spontaneously reported data should be redesigned when applied to event monitoring in drug cohorts.*"

Prescription-event monitoring (PEM) is a proactive, non-interventional method for drug safety monitoring.[1]

The Drug Safety Research Unit (DSRU) data warehouse has accumulated information on 91 complete PEM studies, for which 5.2 million prescriptions were collected, corresponding to >1.1 million green forms being processed. Events are coded using an in-house hierarchical dictionary. An event is "defined as any new diagnosis or reason for referral to a consultant, an admission to hospital, any unexpected deterioration or improvement in a concurrent illness, any suspected adverse drug reaction, any alteration of clinical importance or any complaint considered sufficiently relevant to enter the patient notes".[1]

Differences between PEM and spontaneous reporting systems that are relevant for signal detection include: (i) PEM collects all events regardless of their suspected causal link to the drug, their expectedness, seriousness or frequency; (ii) the general practitioner (GP) is encouraged to report without being asked to assess suspicion or causality. These differences do strengthen signal detection since: (i) the information corresponds to real-life drug use; (ii) the follow-up over time supports the production of a person-time denominator allowing for the calculation of event incidence rates; (iii) the information is collected and coded in an standardized and uniform way which improves data quality; (iv) the drugs are studied shortly after their introduction into the market.

1. Signal Detection in Prescription Event Monitoring

Two main types of signal-detection methods are implemented at the DSRU, namely qualitative and quantitative methods. The qualitative methods rely on the astute clinical evaluation of the information returned by the GP. It aims to identify clues of causality, unexpected events and events to target for follow-up. The quantitative methods consist of calculations based on the frequency of the events and the duration of patient exposure to the drug.

Incidence density differences compare the incidence of an event between two distinct periods of the observation time; for example, the first month and the remaining 5 months, in a 6-month follow-up cohort. Positive significant differences highlight events with higher incidence in the first period, indicating an event with early onset. On the other hand, negative differences highlight a potential delayed reaction, that is, a higher incidence in the second period.

The incidence rate ratio (IRR) is a disproportionality measurement that compares the incidence of a particular event in a drug cohort with the incidence for that same event in a comparator group of other drug cohorts for which PEM studies have been conducted.

An additional disproportionality assessment is undertaken through the use of proportional reporting ratios (PRRs), with statistical significance tested by the Chi-square (χ^2) test. PRRs are particularly helpful in datasets with a high proportion of missing values for date of stopping therapy or the date of event onset. They are also helpful in studying drugs with pro re nata therapeutic regimens for which the exposure is not homogeneous over time.

Previous work using PRRs in PEM focused on the choice of comparator groups and the effect of dictionary levels.[2] The present study looked into the effect of multiple events in the same person on the PRR calculation when used to data mine cohort data.

2. Multiple Events and Proportional Reporting Ratios

Consider two hypothetical drugs, X and Y, for which a cohort of exposed patients has been collected. If the drug X is indicated to treat a condition associated with high morbidity, the patients in the cohort are expected to have numerous events during the follow-up time. This higher number of events per patient would affect the calculation of the PRR by increasing the count for 'all other events' in the contingency table as proposed by Evans et al.[3] and subsequently decreasing the value of the PRR. In comparison, the drug Y, a drug indicated for disease prevention, will be expected to have a lower morbidity, i.e. on average fewer events reported for individual patients. The expected effect is an inflated PRR

value since there are a smaller number of 'all other events'.

The distribution of multiple events reported per person revealed substantial discrepancies among the 91 drugs for which PEM studies have been completed. The differences between drugs were not, however, explained by the median age of the cohorts.

3. Events versus Cases

To study the above mentioned effect, the calculation of PRRs based on events[3] was compared with that based on cases, as used by van Puijenbroek et al.[4] The difference dwells in the fact that the event-based calculation includes the counts of 'all other events', disregarding their dependency when occurring in the same patient; however, the case-based calculation follows a binomial logic separating those patients who present the event of interest and those who don't, disregarding the number of other events reported.

To compare the two calculation methods, ten drugs were selected using a set of arbitrary criteria (cohort completed in 1999 or 2000, medicines that are used continuously, and had a follow-up time of 6 months). The group of ten cohorts were not significantly different from the background comparator group of 81 drugs with regard to cohort size, median age and therapeutic class.

Three of the ten drug cohorts presented a high proportion of patients with a very low number of events, mostly single events. For these three drugs, the event-based PRR was systematically higher than the case-based PRR when reviewing the median difference between the PRRs for each reported drug-event combination.

The differences between the PRR value for the two calculation methods was more striking when there was a low number of occurrences, i.e. combinations with a smaller number of reports.

Based on the threshold PRR, χ^2 value and number of cases used at the DSRU (PRR $\geq$1.5, $\chi^2 \geq 4$ and n >3) for disproportionality analysis, the agreement between the PRR calculation methods was studied using the Jaccard coefficient of numerical taxonomy (S). The coefficient represents the proportion of combinations where both methods agree out of all the associations highlighted by at least one of the methods.[5]

Despite the high level of agreement between the calculation methods across the ten drugs, the level of concordance was lower for the drugs with more extreme distributions of events per person including the three referred above.

In conclusion, disproportionality techniques created to review spontaneously reported data should be redesigned when used to analyse cohort safety information. The distribution of the number of events reported for the same person may affect the comparison of the strength of signals across drugs studied by PEM using event-based PRRs. The effect is stronger for rarely reported combinations and for high values of PRR. Disproportionality analysis in the context of event reporting methodologies, such as PEM, benefit from a case/non-case design.

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