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Data Mining in Pharmacovigilance – Detecting the Unexpected

The Role of Index of Suspicion of the Reporter

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Abstract

Background: One of the most important aims of pharmacovigilance is to detect signals of adverse drug reactions (ADRs) as early as possible. However, some ADRs are difficult to detect, one example being so called 'type C' reactions. These are effects that present as seemingly 'spontaneous' diseases occurring during treatment with a drug, such as the occurrence of a cardiovascular event while the patient is taking rofecoxib. As this type of ADR is often mistaken for a spontaneous disease, the causative agent may appear as an innocent bystander.

Objective: The primary aim of this study was to investigate the possibility of using data mining approaches to detect signals of 'type C' reactions. We hypothesized that by including concomitant, and not only suspected medications in the calculations of disproportionality analyses, we would be able to identify such reactions.

Study design: We used data from the Swedish Drug Information System, SWEDIS, which contains spontaneous reports submitted by Swedish physicians to the Swedish Medical Products Agency, and applied Bayesian confidence propagation neural network (BCPNN) methodology to calculate the information component (IC) value for drug-event combinations for drugs belonging to the Anatomic Therapeutic Chemical (ATC) classes cardiovascular system, musculoskeletal system and nervous system (number of reports = 51 270) where only the suspected drug was considered, and also where both concomitant and suspected drugs were considered. We then classified drug-event combinations that were signalled by a statistically significantly raised IC value as labelled or unlabelled based on the approved summary of product characteristics (SPC) in Sweden as of November 2007, and further classified them as 'type C' reactions or not 'type C'.

Main outcome measure: The proportion of 'type C' reactions signalled when considering both concomitant and suspected drugs compared with suspected drugs only.

Results: The proportion of labelled drug-event combinations when considering suspected drugs was 78.6%. Drug-event combinations classified as 'type C' reactions were more likely to be found when considering both concomitant and suspected drugs compared with suspected drugs only; 18/449 versus 0/248 when considering drug-event combinations that were signalled exclusively by one of the approaches. Such drug-event combinations included, for example, sudden death and celecoxib, myocardial infarction and diclofenac, suicide-related events and several antidepressants.

Conclusion: Including both concomitant and suspected drugs in data mining practices may be a way of detecting 'type C' reactions earlier. This could constitute an advance in data mining for pharmacovigilance practices.

Background

One of the major aims of pharmacovigilance is to detect signals of adverse drug reactions (ADRs) as early as possible and with minimum patient exposure.[1,2] Spontaneous reporting of possible ADRs by healthcare providers to regulatory agencies or drug companies is an important feature of postmarketing pharmacovigilance. Such reports have traditionally been manually reviewed and entered into databases, but since the flow of ADR reports is constantly growing, computer-assisted signal detection algorithms ('data mining' algorithms) have been developed to assist the reviewer in the detection of potential signals.[3,4] Such methods are usually designed to detect drug-event combinations in excess of what would be expected if the drug and event were independently distributed in the database (so-called 'disproportionality analyses'). As the control group, the background frequency of drugs and events in the whole database is used, whereby an observed to expected ratio for each drug-event combination is determined.[1,4,5] Once a statistically significant disproportionality has been detected by such methods, the evidence for a causal association between the drug and the event is reviewed by a clinical expert, thereby helping to assist in the timely detection of a new signal. Many disproportionality analysis methods have been developed, such as the Bayesian confidence propagation neural network (BCPNN) methodology, empirical Bayes screening (EBS), reporting odds ratios (RORs) and incidence rate ratios (IRRs), cumulative sum (cusum) techniques, time scans, Poisson distribution methods, and proportional reporting ratios (PRRs).[4] None of these methods has been prospectively evaluated, and there is no gold standard.

Missed or delayed signalling of important events can have significant consequences on public health, as exemplified by the association between serious cardiovascular events and cyclooxygenase-2 selective inhibitors ('coxibs').[6-10] This particular type of ADR is one of the most difficult to detect. In principle, there are two distinct groups of ADR, known as 'type A' and 'type B' reactions. 'Type A' reactions are effects that are related to the pharmacological effects of the drug, are dosage-related, and therefore most are relatively easy to detect since they may be predicted.[11] 'Type B' reactions are effects that are often allergic or idiosyncratic reactions, characteristically occurring in only a minority of patients and usually unrelated to dosage; they are often serious, unexpected and unpredictable.[11] However, so-called 'type C' reactions are effects related to an increased frequency of seemingly 'spontaneous' diseases that occur during treatment with a drug. In essence, 'type C' reactions are usually ADRs mistaken for 'spontaneous' and 'expected' events occurring in the studied population.[11] The example of cardiovascular events associated with coxib use can be said to represent a typical example of such an event,[7,9,10] where it was necessary to rely on large clinical

investigations to confirm the ADR. Thus, 'type C' reactions are, as a rule, more difficult to detect than reactions of 'type A' and 'type B' due to the lack of a clear temporal association and that the reaction also precipitates a disease that may often arise spontaneously. Usually, large randomized controlled trials, meta-analyses, or large-scale retrospective observational studies utilizing data from electronic health records or medical insurance-claims databases are required for their detection. Signals of such reactions are often delayed and the drug may have been approved by health authorities and marketed for some time.

Objective

The primary aim of this study was to investigate the possibility of detecting signals of a 'type C' reaction in a database of spontaneous ADR reports that is moderately sized compared with the large US FDA and WHO databases. To do this, we included not only suspected, but also concomitant medications in the calculations of disproportionality analyses. In order to investigate whether this may be useful in detecting 'type C' reactions, we included truly unexpected drug-event combinations where a concomitant agent had been mistaken for an innocent bystander. This is a characteristic of 'type C' reactions and, to our knowledge, this has not been previously described, although the approach of not distinguishing between suspected and non-suspected medications as such has previously been utilized.[12] Since no investigation of the performance of BCPNN has been undertaken in ADR databases other than those of considerable size, a secondary aim was to evaluate if BCPNN can also be a useful tool in databases of moderate size.

Study Design

We used data from the Swedish Drug Information System, SWEDIS.[13] This database contains spontaneous reports submitted since 1965 by Swedish physicians to the Swedish Medical Products Agency. As of 31 March 2007, there were in total 102 728 reports in the database. In SWEDIS, a Swedish dictionary is used for coding ADRs. It is built on a three-level hierarchical structure and was developed by the Medical Products Agency. The first level is the system organ class, followed by group terms, and finally preferred terms. The dictionary holds a little over 1000 preferred terms. We have recently applied data mining methods to this database, specifically the BCPNN method.[14] For the purpose of this study, and in order to arrive at a manageable number of drug-event combinations, only reports involving the Anatomic Therapeutic Chemical (ATC) classes cardiovascular system, musculoskeletal system and nervous system, either as a suspected or as a concomitant agent, were considered (number of reports = 51 270). The choice of these particular ATC classes was made because they had been involved in a significant number of safety issues during recent years at our Agency, and three different classes were chosen to increase the generalizability of the results to the entire database.

The information component (IC) value for all combinations of a specific drug at ATC level 7 (substance level) and a specific event at the preferred term level was calculated. We created two groups of calculations, one for drug-event combinations where only the suspected drug was considered in the observed count, and one where both concomitant and suspected drugs were considered. Each drug-event combination with a significantly raised IC value (IC >0; lower 95% CI >0; number of reports ≥3), henceforth called 'signal of disproportionate reporting' (SDR), was then compared with the approved summary of product characteristics (SPC) in Sweden as of November 2007 for the drug in question and classified as labelled or unlabelled; thus, only currently approved drugs were considered. An SDR when considering only suspected drugs (SDR[Suspected]) and an SDR when considering both suspected and concomitant drugs (SDR[Total]) was considered labelled if it was mentioned anywhere in the SPC as a possible ADR. Medical Dictionary for Regulatory Activities (MedDRA) terminology was consulted on those occasions when there was uncertainty whether an event should be considered labelled or

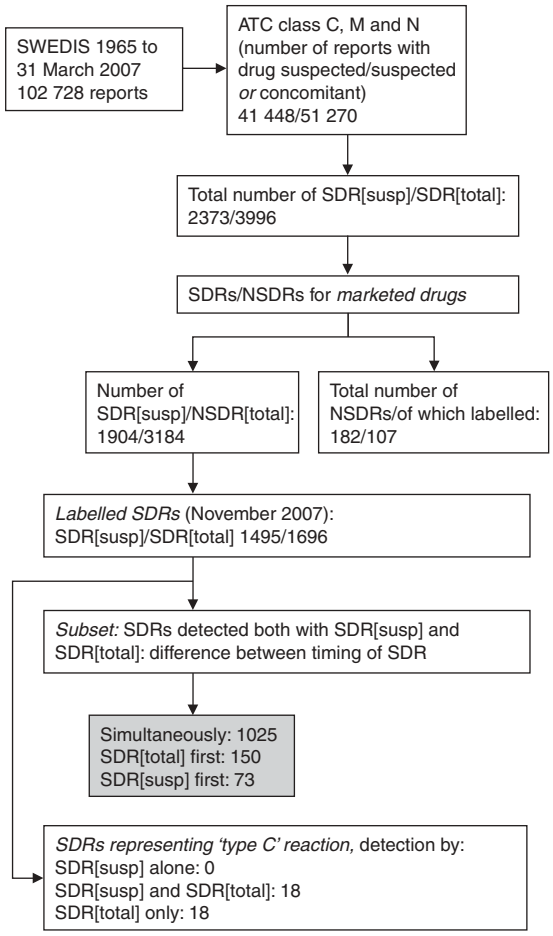

Fig. 1. Selection process and overview of results. **ATC** = Anatomical Therapeutic Chemical (codes: **C** [cardiovascular system], **M** [musculoskeletal system] and **N** [nervous system]); **NSDR** = negative signal of disproportionate reporting; **SDR** = signal of disproportionate reporting; **susp** = suspected; **SWEDIS** = Swedish Drug Information System.

not. When labelled reactions could be considered clinically more pronounced (e.g. vomiting) than a signalled reaction (e.g. nausea), the latter was considered labelled. No qualitative review of individual reports was performed, as the aim of the study was to look at the relationship between positive SDRs and labelling status. The proportion of labelled SDRs was then determined and compared between the two groups.

We also compared the year and quarter at which the IC value was first significantly raised in each group, by a retrospective investigation of SWEDIS. In addition, we determined the proportion of labelled drug-event combinations with a significantly negative IC value (upper 95% CI <0; number of reports ≥3), henceforth called 'Negative Signal of Disproportionate Reporting' (NSDR), and compared this proportion with that of SDR[Suspected] in order to evaluate the performance of BCPNN in this database. We finally reviewed all labelled SDRs in the two groups, classified them as 'type C' reactions or 'non-type C' reactions, and compared the proportion of such reactions between the groups.

Differences in proportions and means were calculated with 95% confidence intervals. When a signalled and labelled reaction was considered a 'type C' reaction by the investigators, we performed a search of PubMed and the home pages of the Swedish and British medicines regulatory authorities (the Swedish Medical Products Agency[15] and Medicines and Healthcare products Regulatory Agency,[16] respectively) to substantiate the classification. Search terms were

Table I. The number of drugs approved in Sweden and reported to the Swedish Drug Information System (SWEDIS) as of 31 March 2007, stratified by Anatomical Therapeutic Chemical (ATC) class

ATC code (class)[a]	Number of different drugs (% of all drugs)[a]
A (alimentary tract and metabolism)	253 (12.6)
B (blood and blood-forming organs)	102 (5.1)
C (cardiovascular system)	220 (11.0)
D (dermatologicals)	126 (6.3)
G (genitourinary system and sex hormones)	130 (6.5)
H (systemic hormonal preparations, excluding sex hormones and insulins)	49 (2.4)
J (anti-infectives for systemic use)	256 (12.7)
L (antineoplastic and immunomodulating agents)	138 (6.9)
M (musculoskeletal system)	86 (4.3)
N (nervous system)	306 (15.2)
P (antiparasitic products, insecticides and repellents)	40 (2.0)
R (respiratory system)	127 (6.3)
S (sensory organs)	72 (3.6)
V (various)	103 (5.1)
All ATC classes	2008

a A total of 340 different herbal preparations or non-licensed preparations without an ATC code are not included in the table.

Table II. The number of signals of disproportionate reporting (SDRs) in each of the Anatomical Therapeutic Chemical (ATC) classes C (cardiovascular), M (musculoskeletal) and N (nervous system) as of 31 March 2007 in the Swedish Drug Information System (SWEDIS)

ATC code	Total number of reports in SWEDIS (Suspected/Total)	SDR[Suspected] [n/n labelled (%)][a]	SDR[Total] [n/n labelled (%)]	Difference in proportion labelled [% (95% CI)]
C	13 753/23 660	544/405 (74.4)	1134/456 (40.2)	34.2 (29.6, 38.9)
M	9 076/12 727	337/281 (83.4)	429/279 (65.0)	18.3 (12.3, 24.4)
N	19 772/27 419	1023/809 (79.1)	1621/961 (59.3)	19.8 (16.3, 23.3)
C, M and N	41 448/51 270	1904/1495 (78.5)	3184/1696 (53.3)	25.2 (22.7, 27.8)

a Labelling was determined from the approved Swedish SPC as of November 2007. The table shows two groups; concomitant + suspected SDRs [Total], and suspected SDRs only [Suspected].

n = number; **SPC** = summary of product charcteristics.

individual drug names as well as drug class names in combination with the adverse event in question. In figure 1, the different steps in the selection process are depicted, as well as an overview of the results of the study.

Main Outcome Measure

The main outcome measure was proportion of 'type C' reactions signalled when considering both concomitant and suspected drugs compared with suspected drugs only.

Results

Proportion of Labelled Signals of Disproportionate Reporting

The number of drugs reported to SWEDIS as of 31 March 2007, stratified by ATC class, are shown in table I. In total, 2373 SDR[Suspected] were identified, and 3996 SDR[Total]. Table II shows the number of SDRs in each of the two groups, SDR[Suspected] and SDR[Total], in which the reported drugs were still on the market in November 2007. The proportion of labelled SDR[Suspected] was 78.5% overall, and was significantly lower, 53.3%, when considering SDR[Total] (difference 25.2%; 95% CI 22.7, 27.8), although the latter approach detected a larger absolute number of labelled SDRs. Table III shows the proportion of labelled SDRs[Suspected] (1904/1495; 78.5%), compared with the proportion of NSDRs[Suspected] (107/182; 58.8%). The difference in proportion was 19.7% (95% CI 12.3, 27.1).

Table IV shows the difference in timing of SDRs depending on inclusion (SDR[Total]) or non-inclusion (SDR[Suspected]) of drugs reported as concomitant and not suspected in the ADR report. The comparison is restricted to those combinations that presented an SDR for both calculations at the end of the study period. For all ATC classes in the analysis, the proportion of SDR[Total] that occurred before the SDR[Suspected] was significantly higher than the proportion of SDR[Suspected] that occurred before the SDR[Total]. Furthermore, the difference in timing expressed as the average number of years between occurrence of the first SDR[Total]

Table III. Proportion of signals of disproportionate reporting (SDRs)[Suspected] with lower 95% CI >0 compared with the proportion of negative SDRs (NSDRs)[Suspected] with upper 95% CI <0

ATC code	SDR[Suspected] with lower 95% CI >0 (n)	Labelled SDR[Suspected] [n (%)]	NSDR[Suspected] with upper 95% CI <0 (n)	Labelled NSDR[Suspected] [n (%)]	Difference in proportion labelled [% (95% CI)]
C	544	405 (74.4)	65	38 (58.5)	15.9 (3.5, 28.5)
M	337	281 (83.4)	27	15 (55.6)	27.8 (8.7, 47.0)
N	1023	809 (79.1)	90	54 (60.0)	19.1 (8.7, 29.5)
Total	1904	1495 (78.5)	182	107 (58.8)	19.7 (12.3, 27.1)

ATC = Anatomical Therapeutic Chemical; **C** = ATC class 'cardiovascular system'; **M** = ATC class 'musculoskeletal system'; **N** = ATC class 'nervous system'; **n** = number.

Table IV. Comparison of timing of labelled signals of disproportionate reporting (SDRs) using suspected+concomitant drugs (SDR[Total]) and suspected drugs only (SDR[Suspected])

ATC code	Labelled SDRs (n)[a]	Simultaneously detected SDRs [n (%)]	SDR[Total] before SDR[Suspected] [n (%)]	Average difference in timing [y (1 SD)]	SDR[Suspected] before SDR[Total] [n (%)]	Average difference in timing [y (1 SD)]	Difference in proportion SDR[Total]-SDR[Suspected] [% (95% CI)]	Difference in timing SDR[Total]-SDR[Suspected] [y (95% CI)]
C	311	241 (77.5)	43 (13.8)	3.7 (3.6)	27 (8.7)	1.7 (1.3)	5.1 (0.2, 10.1)	2.0 (0.6, 3.5)
M	225	196 (87.1)	22 (9.8)	4.4 (4.0)	7 (3.1)	2.3 (2.4)	6.7 (2.2, 11.2)	2.1 (–1.1, 5.4)
N	712	588 (82.2)	85 (11.9)	2.8 (2.8)	39 (5.5)	1.7 (1.5)	6.4 (3.6, 9.4)	1.1 (0.1, 2.1)
Total	1248	1025 (82.1)	150 (12.0)	3.3 (3.3)	73 (5.8)	1.8 (1.6)	6.2 (3.9, 8.4)	1.5 (0.7, 2.3)

a Restriction to those combinations that presented an SDR for both calculations at the end of the study period.

ATC = Anatomical Therapeutic Chemical; **C** = ATC class 'cardiovascular system'; **M** = ATC class 'musculoskeletal system'; **N** = ATC class 'nervous system'; **n** = number; **SD** = standard deviation.

and the first SDR[Suspected] was statistically significant for two of three ATC classes. SDRs occurring first for the SDR[Total] calculation were, on average, significantly earlier than for SDRs occurring first for SDR[Suspected], with the largest difference for ATC code C: 2.0 years (95% CI 0.6, 3.5).

'Type C' Reactions

Table V shows both labelled SDRs[Suspected] and SDRs[Total] identified as possible 'type C' reactions. Such reactions were more likely to be found in the latter case (18/449 vs 0/248 when considering SDRs that were signalled exclusively by one of the approaches).

Discussion

This study shows that nearly 80% of all SDRs in SWEDIS were labelled when screening was performed using the standard approach of considering only suspected drugs. This was significantly different from NSDRs, which were labelled on about 60% of occasions. This type of large-scale validation of a data mining tool has, to our knowledge, not been previously performed. It is therefore encouraging to find evidence suggesting that data mining, even in a database of moderate size such as SWEDIS, may be a useful tool in pharmacovigilance. SDRs[Total] compared with SDRs[Suspected] exhibited a lower specificity, although the absolute number of detected SDRs was higher. Furthermore, the timepoint of those SDRs that were labelled was significantly earlier for SDRs[Total]. Of particular interest, is the observation that SDRs[Total] signalled SDRs characteristic of 'type C' reactions significantly more frequently than did the traditional methodology of only considering SDRs[Suspected] where the drug was suspected as causative. SDRs of this type included, for example, sudden death during treatment with celecoxib,[7,9,10] myocardial infarction during treatment with diclofenac[6,8] and suicide-related events during treatment with several antidepressants.[25,27] The choice between using SDRs[Suspected] and SDRs[Total] may

Table V. Labelled signals of disproportionate reporting (SDRs) considered as potential 'type C' reactions. All reactions had a significantly raised information component value detected when considering the drug suspected, concomitant or both. Citations are to studies or other documentation supporting the 'type C' characteristics of the reactions

ATC code	SDR[Suspected] alone	SDR[Total] *and* SDR[Suspected]	SDR[Total] alone
C	None	None	Doxazosin – haemorrhage[17,18]
M	None	Celecoxib – myocardial infarction[7,9,10]	Risedronic acid – osteonecrosis[19,20]
		Etoricoxib – myocardial infarction[7]/ cerebral infarction[7]	Diclofenac – myocardial infarction[6,8]
			Ketoprofen – myocardial infarction[6-8]
			Celecoxib – mors subita[7,9,10]
N	None	Levomepromazine – mors subita[21]	Levomepromazine – death[21]
		Clozapine – pulmonary embolism[22]/ hyperglycaemia[23]/diabetes mellitus[23]	Haloperidol – death[21]/mors subita[21]
		Olanzapine – death[21]/mors subita[21]/ hyperglycaemia[23]/diabetes mellitus[23]/ hyperlipaemia[23]	Clozapine – cerebral infarction[24]
		Citalopram – suicide attempt[25,27]	Olanzapine – thrombosis venous leg[22]
		Paroxetine – suicide attempt[25,27]	Lithium – vascular malformation[26]
		Moclobemide – suicide[25,27]	Amitriptyline – thoughts of suicide/suicide[25,27]
		Duloxetine – thoughts of suicide[25,27]	Citalopram – condition aggravated/suicide[25,27]
		Atomoxetine – depressed mood[28]	Mirtazapine – suicide[25,27]
		Bupropion – depressed mood[25,27]	Venlafaxine – suicide[25,27]
			Galantamine – myocardial infarction[29]
Total no. of SDRs	0	18	18

ATC = Anatomical Therapeutic Chemical; **C** = ATC class 'cardiovascular system'; **M** = ATC class 'musculoskeletal system'; **N** = ATC class 'nervous system'; **n** = number.

therefore be influenced by a number of factors, including (i) the overall workload of SDRs for a drug, i.e. SDRs[Total] may be preferred if the number of SDRs is low, in order to increase sensitivity, whereas SDRs[Suspected] may be better where the number of SDRs is high and available pharmacovigilance resources are limited; (ii) the overall risk-benefit profile for a drug, e.g. a serious type C reaction will probably have a more profound effect on the risk-benefit profile for a cough remedy than for an oncology drug; and (iii) whether or not a drug is used by a large number of patients, and the general health of these patients.

Much routine data mining focuses on the count of SDRs where the reporters have attributed suspicion to avoid some false positives.[30] However, in the quest for as much objectivity as possible it makes intuitive sense to include counts of SDRs regardless of suspicion as cases of interest. Thus, to discover the truly unexpected, drugs that even the reporter has not suspected as a culprit of disease, should perhaps be considered. As exemplified by the withdrawal of rofecoxib due to an increased risk of cardiovascular events,[31] this type of ADR is one of the most difficult to detect, as the event is often mistaken for a spontaneous disease, making the causative agent appear as an innocent bystander – characteristics that are typical for 'type C' reactions.[11]

Some limitations of this study should be discussed. Firstly, SDRs were considered true or false according to the approved Swedish SPCs. Some ADRs will be labelled but the causal link between drug and adverse event may still be questioned; conversely, unlabelled ADRs highlighted by data mining calculations may not necessarily be false, but represent very rare ADRs that have not yet been detected. This definition of what is or is not an established ADR could affect the assessments of the proportions of labelled SDRs in this study. Secondly, the high proportion of labelled SDRs observed in this study may have been affected by publication bias; it was

not possible to obtain data regarding dates for labelling changes to examine this possibility. However, any influence of publication bias on the difference between SDR[Suspected] and SDR[Total] would be likely to reduce the observed difference between the two methodologies, thus rendering this potential bias of lesser importance. Thirdly, as a 'type C' reaction is defined as one that resembles a spontaneous disease, its definition gives room for subjective interpretations. Thus, the classification of an SDR as a 'type C' reaction is influenced by subjective assessment and may differ between assessors. However, we consider the difference in proportion of unique SDRs assessed as 'type C' reactions between SDRs[Total] and SDRs[Suspected] as sufficiently large to consider the two approaches relevantly different. Fourthly, as only the ATC classes C, N and M were investigated in this study, it is not fully certain that the results can be generalized to all ATC classes.

Conclusions

We conclude that data mining with BCPNN can be a useful tool in pharmacovigilance, even in databases of moderate size, with an almost 80% chance of an SDR[Suspected] being labelled. We further conclude that taking into consideration both concomitant and suspected drugs in data mining practices may be a way of detecting 'type C' reactions earlier, at least in a database the size of SWEDIS. This could constitute an advance in data mining for pharmacovigilance practices. Further work would be needed to generalize this finding to datasets of different sizes.

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