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Effect of Competition Bias in Safety Signal Generation

Analysis of a Research Database of Spontaneous Reports in France

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Abstract

Background: Automated disproportionality analysis of spontaneous reporting is increasingly used routinely. It can theoretically be influenced by a competition bias for signal detection owing to the presence of reports related to well-established drug-event associations.

Objective: The aim of the study was to explore the effects of competition bias on safety signals generated from a large spontaneous reporting research database.

Methods: Using the case/non-case approach in the French spontaneous reporting research database, which includes data of reporting in France from January 1986 to December 2001, the effects of the competition bias were explored by generating safety signals associated with six events of interest (gastric and oesophageal haemorrhages, central nervous system haemorrhage and cerebrovascular accidents, ischaemic coronary disorders, migraine headaches, muscle pains, and hepatic enzymes and function abnormalities) before and after removing from the database reports relating to drugs known to be strongly associated with these events, whether they constituted cases or non-cases. As this study was performed on a closed database (last data entered 31 December 2001), potential signals unmasked by removal were considered as real signals if no or only incomplete knowledge about the association was available from the literature before 1 January 2002.

Results: For gastric and oesophageal haemorrhages, after removing reports involving antithrombotic agents or NSAIDs, three potential signals were unmasked (prednisone, rivastigmine and isotretinoin). For central nervous system haemorrhage and cerebrovascular accidents, after removing reports involving antithrombotic agents, three potential signals were unmasked

(ethinylestradiol, interferon-α-2B and methylprednisolone). For ischaemic coronary disorders, after removing reports involving anthracyclines, bleomycine, anti-HIV drugs or triptans, one potential signal was unmasked (ondansetron). For migraine headaches, after removing reports involving nitrates, calcium channel blockers, opioid analgesics or intravenous immunoglobulins, six potential signals were unmasked (ammonium chloride, leflunomide, milnacipran, montelukast, proguanil and pyridostigmine). For muscle pains, after removing reports involving statins or fibrates, seven potential signals were unmasked (hydroxychloroquine, lactulose, levodopa in combination with dopadecarboxylase inhibitor, nevirapine, nomegestrol, ritonavir and stavudine). Finally, for hepatic enzymes and function abnormalities, after removing reports involving NSAIDs, anilides, antituberculosis drugs, antiepileptics, ketoconazole, tacrine, or amineptine, two potential signals were unmasked (caffeine, metformin). Of all these unmasked potential signals, ten appeared non/incompletely documented as at 1 January 2002 and were considered as real signals, with three of these later being confirmed by the literature and finally considered as true positives (isotretinoin, methylprednisolone and milnacipran).

Conclusion: This study confirms that a competition bias can occur when performing safety signal generation in spontaneous reporting databases. The minimization of this bias could lead to previously masked signals being revealed.

Background

Spontaneous reporting of adverse drug reactions (ADRs) is a standard and generalized method of identifying safety signals for marketed drugs.[1-3] Its primary purpose is to provide early warnings of ADRs not recognized prior to marketing. Once a signal has been identified, other methods may be needed to quantify the potential risk and if there is sufficient evidence of a public health issue, steps may be taken by regulatory authorities. To improve the capacity of spontaneous reporting systems to detect signals in the crowd of an increasingly large number of reports, various data-mining methods have been devised to test for reporting disproportionality, i.e. that a drug-event pair is reported more often than would be expected. They include Bayesian exploration, neural networks, information content and reporting rates ratio, whether the computation is based on the relative risk, as for the proportional reporting ratio, or the odds ratio (OR), as for the case/non-case approach reporting OR (ROR). These methods are all essentially based on the disproportionality of the reporting of a given event with a given drug (or class of drugs) compared with other events and other drugs, and may differ in sensitivity or specificity but mostly give similar results when the number of reports exceeds three.[4] However, independently of the method employed, disproportionality analyses in large spontaneous reporting databases are generally plagued by a prohibitive flood of false positives (spurious signals) and known drug-event associations that congest the system. On the other hand, weaker but relevant signals may be missed because of competitive signal generation.

The signal being detected in disproportionality analysis is a ratio, and thus depends on both the numerator, which concerns only reports involving the drug of interest, and the denominator, which concerns reports involving other drugs. Although most discussions focus on biases that affect the numerator, such as those related to reporting of reactions to the drug of interest,[5-8] the denominator may also be subject to bias. For

example, if the event was significantly associated with other drugs, this will inflate the denominator by increasing the background reporting rate, thereby possibly decreasing the sensitivity of the signal generation process. This competition bias was approached for hypothetical newly marketed drugs in a previous paper using mathematical simulations;[9] it is similar to the masking phenomenon that had also been pointed out in the literature.[10,11]

To further investigate the consequences of such a bias on the detection of safety signals, we wanted to study which signals could have been plagued by such a potential competition bias, using a large spontaneous reporting database, dedicated to research, and gathering all data from 16 years of spontaneous reporting in France.

Methods

Study Design and Source of Data

A case/non-case automated disproportionality analysis[4] was performed using data from the French Pharmacovigilance Database, which includes all ADRs reported to the French Regional Pharmacovigilance Centres since 1985.[12] Reactions are coded according to the WHO Adverse Reaction Terminology (WHO-ART) dictionary. The study used a closed research database extracted from the main national pharmacovigilance database that has been cleaned and fully verified for coding errors and which contains reports that occurred between January 1986 and December 2001.[13] This gives a 10-year period of additional literature to help evaluate signals that may have been controversial at the time of the last reports. All ADRs included in the original reports have been recoded according to the Medical Dictionary for Regulatory Activities (MedDRA® Version 3 [MedDRA® 3]) classification. MedDRA® terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). All drugs have been recoded according to the Anatomical Therapeutic Chemical (ATC) classification.

Events of Interest

Signal generation was performed for six high-level terms (HLTs)[14] of the MedDRA® classification thought to represent various types of ADRs: (i) gastric and oesophageal haemorrhages; (ii) central nervous system haemorrhage and cerebrovascular accidents; (iii) ischaemic coronary artery disorders; (iv) migraine headaches; (v) muscle pains; and (vi) hepatic enzymes and function abnormalities.

Case Definition and Identification

For each event of interest, we classified as cases all reports mentioning at least one ADR related to the event of interest according to MedDRA® 3 classification. Non-cases were defined as reports that did not mention an ADR related to the event of interest according to the MedDRA® 3 classification.

Definition and Identification of Reports to Remove from the Database

For each event of interest, we removed from the database all reports mentioning at least one of the main drugs known to be associated with the studied event. First, for each event of interest, from *Meyler's side effects of drugs*, *14th edition*,[15] and expert assessment we identified the main drugs known to be associated with the event; this identification was performed *a priori* before any signal detection was performed in the present study. The list of these drugs, with the corresponding ATC codes, is detailed in table I for each HLT and related ADR of interest. Second, for each event of interest, all reports for which at least one drug corresponding to a drug known to be associated with the event was identified were removed from the database, whether cases or non-cases.

Statistical Analysis and Data-Mining Computing

All statistical techniques that can be used for signal generation from spontaneous reporting databases have been shown to provide similar results when the number of cases associated with a given drug exceeds three (i.e. four or more

Table I. List of the main drugs known to be associated with the event of interest for each studied event, with corresponding Anatomical Therapeutic Chemical codes

MedDRA® HLTs used in spontaneous reports	Main drugs associated with the related ADRs	ATC codes
Gastric and oesophageal haemorrhages	Antithrombotic agents[a]	B01, N02BA01, A01AD05, S01XA13, S01XA14
	Antiinflammatory and antirheumatic products, non-corticosteroids	M01A, M01B
Central nervous system haemorrhage and cerebrovascular accidents	Antithrombotic agents[a]	B01, N02BA01, A01AD05, S01XA13, S01XA14
Ischaemic coronary artery disorders	Anthracyclines and related substances	L01DB
	Bleomycine,	L01DC01
	Antiretroviral HIV drugs	J05AE, J05AF, J05AG
	Selective serotonin 5-HT_1 agonists (triptans)	N02CC
Migraine headaches	Nitrate derivatives	C01DA
	Calcium channel blockers	C08
	Opioid analgesics	N02A
	Intravenous immunoglobulins	J06BA
Muscle pains	Statins	C10AA, C10B
	Fibrates	C10AB
Hepatic enzymes and function abnormalities	Antiinflammatory and antirheumatic products, non-corticosteroids	M01A, M01B
	Anilides	N02BE
	Other analgesics and antipyretics	N02BG
	Antibiotics for the treatment of tuberculosis	J04AB
	Antiepileptics	N03
	Ketoconazole	J02AB02, G01AF11, D01AC08
	Tacrine	N06DA01
	Amineptine	N06AA19

a Including antiplatelet agents, anticoagulant agents, thrombolytic agents.

ADRs = adverse drug reactions; **ATC** = Anatomical Therapeutic Chemical; **HLTs** = high-level terms.

exposed cases).[4] Moreover, it is considered that a signal that would be statistically generated from a number of exposed cases lower than three should not be considered. In this study, the data-mining algorithm chosen for the analyses was the ROR of the case/non-case method.[16] The ROR relates the proportional representation of a reaction of interest to a drug of interest compared with the proportional representation of that reaction among all other drugs in the database. In the case/non-case method, the ROR is estimated with its 95% confidence interval (CI). A signal is considered statistically significant when the lower limit (LL) of the 95% CI for the ROR is greater than one. To focus only on potential signals that would have been considered relevant for examination in a routine pharmacovigilance exercise, only drug-event pairs for which the LL of the 95% CI was greater than one, and for which the number of exposed cases was three or more, were selected. For each event of interest, two procedures were performed for the detection of potential signals: the first considering the whole database, and the second the restricted database obtained after removing all the reports mentioning at least one drug known to be associated with the event of interest. By comparing the results of both procedures, potential signals unmasked by the removal were identified.

Perl v5.8.8 programming language was used to automate the computing of the ROR estimation for each drug-event pair, before and after removal of drugs known to be associated with the event of interest.

Literature-Based Assessment of Unmasked Potential Signals

A signal consists of a possible causal relationship between an ADR and a drug, the relationship being unknown or incompletely documented previously.[17] For each unmasked potential signal, MEDLINE was explored using the PubMed MeSH (Medical Subject Heading) terms for the ADR and drug concerned to identify publications related to the identified drug-event associations. The search also included related drugs or related events.

As this methodological study was performed retrospectively on a closed database (last data entered 31 December 2001), unmasked potential signals were considered as real signals if no or only incomplete knowledge about the association was available from the literature before 1 January 2002. From these real signals, those being later confirmed (after 1 January 2002) in the literature were considered as true positives, whereas those that had not been confirmed were considered as false positives.

Results

Signal Detection

Between 1986 and 2001, 207 236 reports of 307 009 different ADRs were entered into the database. This included 3960 reports mentioning gastric and oesophageal haemorrhages, 972 mentioning central nervous system haemorrhage and cerebrovascular accidents, 806 mentioning ischaemic coronary artery disorders, 3638 mentioning migraine headaches, 2885 mentioning muscle pains, and 530 mentioning hepatic enzymes and function abnormalities.

For each event of interest, reports were removed among the cases and non-cases for the products with known associations with the event. The reports that were removed ranged from 3.9% (muscle pains) to 24.9% (gastric and oesophageal haemorrhages) of all reports contained in the database (see table II).

Gastric and Oesophageal Haemorrhages

After removing reports involving antithrombotic agents or NSAIDs, three potential signals were unmasked (table III). These related to prednisone, isotretinoin and rivastigmine. For prednisone, upper gastrointestinal bleeding is a well-known adverse effect; it has been widely reported in the literature and is considered as a type A reaction for corticosteroids.[18,19] For isotretinoin or rivastigmine, no reference before 1 January 2002 was found in MEDLINE. The first publication that was found involving isotretinoin in gastrointestinal bleeding was published in 2006; this publication related to haemorrhagic

Table II. Proportion of cases and non-cases removed by exclusion of the products with known associations to the event, for each of the studied events

Events of interest	Overall [n/N (%)]	Cases [n^*/N^* (%)][a]	Non-cases [$n^\dagger/N^\dagger$ (%)][b]
Gastric and oesophageal haemorrhages	51 627/207 236 (24.9)	2990/3960 (75.5)	48 637/203 276 (23.9)
Central nervous system haemorrhage and cerebrovascular accidents	39 568/207 236 (19.1)	772/972 (79.4)	38 796/206 264 (18.8)
Ischaemic coronary artery disorders	10 128/207 236 (4.9)	216/806 (26.8)	9912/206 430 (4.8)
Migraine headaches	47 459/207 236 (22.9)	832/3638 (22.9)	46 627/203 598 (22.9)
Muscle pains	8152/207 236 (3.9)	632/2885 (21.9)	7520/204 351 (3.7)
Hepatic enzymes and function abnormalities	45 853/207 236 (22.1)	256/530 (48.3)	45 597/206 706 (22.1)

a Number of reports removed (n^*) and total number of reports for cases (N^*).

b Number of reports removed ($n^\dagger$) and total number of reports for non-cases ($N^\dagger$).

Table III. Number of signals detected before, after and eliminated by removal of reports mentioning drugs associated with the event of interest for each studied event

Events of interest	Before removal	Eliminated by removal		Appearing after removal
		Targeted	Non-targeted	
Gastric and oesophageal haemorrhages	49	35	6	3
Central nervous system haemorrhage and cerebrovascular accidents	49	13	33	3
Ischaemic coronary artery disorders	38	18	1	1
Migraine headaches	55	2	15	6
Muscles pains	60	8	5	7
Hepatic enzymes and function abnormalities	19	12	5	2

colitis and rectal bleeding, but not upper gastrointestinal bleeding events.[20] Before 2002, only two publications were found for the association of isotretinoin with bleeding episodes; these publications related to non-gastrointestinal bleedings.[21,22] For rivastigmine, no reference was found in MEDLINE, either before or after 2002. With regard to the identified literature prior to 1 January 2002, unmasked associations relating to isotretinoin and rivastigmine were considered as real signals.

Central Nervous System Haemorrhage and Cerebrovascular Accidents

After removing reports involving antithrombotic agents, three potential signals were unmasked (table III). These signals related to ethinylestradiol, interferon (IFN)-α-2B and methylprednisolone. The association between exposure to ethinylestradiol and the risk of cerebrovascular haemorrhage was already known in 2002; this risk has been estimated to be slightly increased in subjects using oral contraceptives.[23-26] Similarly, before 2002, central nervous system haemorrhage and cerebrovascular accidents involving IFNα-2B had already been reported in the literature.[27-29] The last unmasked potential signal related to methylprednisolone. Corticosteroids have been widely associated with haemorrhagic phenomena as previously mentioned; however, this has mostly related to gastrointestinal bleeding episodes.[19] Conversely, the literature is very sparse regarding cerebrovascular haemorrhage; only one study reporting an association between corticosteroid use and the occurrence of aneurysmal subarachnoid haemorrhage was found, which had been published in 2006.[30] With regard to the identified literature prior to 2002, this unmasked association relating to methylprednisolone was considered as a real signal.

Ischaemic Coronary Artery Disorders

After removing reports involving anthracyclines, bleomycine, anti-HIV drugs or triptans, one potential signal was unmasked that involved ondansetron (table III). In 2002, ondansetron was already known to be implicated in the occurrence of chest pain or myocardial infarction.[31,32] Furthermore, angina was already listed in the US Summary of Product Characteristics for ondansetron in 1992.[31] This unmasked potential signal was thus not considered as a real signal.

Migraine Headaches

After removing reports involving nitrates, calcium channel blockers, opioid analgesics or intravenous immunoglobulins, six potential signals relating to ammonium chloride, leflunomide, milnacipran, montelukast, proguanil and pyridostigmine were unmasked (table III). In 2002, headache was already known to constitute a frequent adverse effect of montelukast.[33,34] Similarly, headache was the most reported adverse event during randomized controlled trials (RCTs) for proguanil in association with atovaquone,[35,36] and one of the most reported for leflunomide.[37,38] Conversely, it was incompletely documented for milnacipran in 2002[39,40] but was completed later.[41] The literature on the safety of pyridostigmine or ammonium chloride is scarce. In a placebo-controlled RCT performed among soldiers working in a desert environment, headache

was the only adverse effect for which incidence was significantly higher in the pyridostigmine group than in the placebo group.[42] For ammonium chloride, no reference indicating potential adverse reactions for migraine/headaches was found. With regards to the identified literature prior to 1 January 2002, unmasked associations relating to milnacipran, pyridostigmine and ammonium chloride were considered as real signals.

Muscle Pains

After removing reports involving statins or fibrates, seven potential signals were unmasked that incriminated hydroxychloroquine, lactulose, levodopa in combination with dopadecarboxylase inhibitor, nevirapine, nomegestrol, ritonavir and stavudine (table III). No reference specifically mentioning muscle pain as an adverse effect of antiretroviral drugs was found, but muscle pain is one of the main symptoms that can be associated with hyperlactataemia, which was already a known adverse effect of nucleoside reverse transcriptase inhibitors (NRTIs) such as stavudine in 2002.[43] We considered that this could also explain the association found for nevirapine and ritonavir, which although belong to other anti-HIV drug classes than NRTIs are prescribed in combinations with NRTIs. Hydroxychloroquine had also been reported with cases of myopathy before 2002.[44,45] Conversely, no reference focusing on muscle pain associated with the use of levodopa in combination with a dopadecarboxylase inhibitor, lactulose or normegestrol was found in the literature, either before or after 2002. These unmasked potential signals were thus considered as real signals.

Hepatic Enzymes and Function Abnormalities

After removing reports involving NSAIDs, anilides, antituberculosis drugs, antiepileptics, ketoconazole, tacrine or amineptine, two potential signals were unmasked that involved caffeine and metformin. No reference was found in MEDLINE mentioning a potential hepatotoxicity of caffeine, either before or after 2002, which was thus considered as a true signal. Although not initially detected, the signal that was unmasked for metformin is consistent with the existing knowledge on the safety of this drug, with numerous publications prior to 2002 focussing on the hepatotoxicity of metformin.[46,47]

Signals that were unmasked for each of the studied events are detailed in table IV.

Discussion

Spontaneous reporting has been a mainstay of pharmacovigilance since the case of thalidomide almost 50 years ago. The number of reports increases regularly in most countries. Spontaneous reporting databases are increasingly larger,

Table IV. Potential signals unmasked after removal of reports mentioning main drugs known to be associated with the event of interest for each of the studied events, according to information available from MEDLINE before and after 1 January 2002

Events of interest	Potential signals unmasked after removal		
	Already known (as at 1 January 2002)	Unknown, later confirmed	Unknown, not later confirmed
Gastric and oesophageal haemorrhages	Prednisone	Isotretinoin	Rivastigmine
Central nervous system haemorrhage and cerebrovascular accidents	Ethinylestradiol, Interferon-α-2B	Methylprednisolone	
Ischaemic coronary artery disorders	Ondansetron		
Migraine headaches	Leflunomide, montelukast, proguanil	Milnacipran	Ammonium chloride, pyridostigmine
Muscles pains	Nevirapine, ritonavir, stavudine,		Hydroxychloroquine, levodopa + dopadecarboxylase inhibitor, lactulose, nomegestrol
Hepatic enzymes and function abnormalities	Metformin		Caffeine

making manual detection of alerts increasingly more difficult. Automated signal generation using disproportionality analysis or data-mining techniques has, in consequence, become increasingly common, with drug agencies and/or pharmaceutical firms increasing reliance on them to identify signals.

In a recent publication,[9] it was demonstrated, using simulations, that a competition bias could occur for the detection of new signals if some strong drug-event associations already existed in spontaneous reporting databases, showing that fully automated searches may not be optimally effective for the detection of safety signals, especially for clinically serious and relatively common events.

The present study illustrates, using a research database including data from more than 15 years of spontaneous reporting in France, what types of signals could have been ignored in the past because of this competition bias. These results are consistent with those of previous studies.[9-11]

For the selected events of interest, the potential safety signals that were unmasked when addressing this bias were consistent with the current safety knowledge on the associated drugs, and could have even provided additional knowledge in some cases and been considered as true signals as at 2002.

Overall, 22 potential signals were unmasked for six events of interest (three for gastric and oesophageal haemorrhages, three for central nervous system haemorrhage and cerebrovascular accidents, one for ischaemic coronary artery disorders, six for migraine headaches, seven for muscle pains, and two for hepatic enzymes and function abnormalities). Of these, ten appeared to constitute real signals as at 1 January 2002, according to the existing literature at this time. Three of these were further confirmed by the literature and should thus be considered as true positive signals, which could have been detected earlier if the competition bias had been minimized as proposed. This was the case for isotretinoin and gastric and oesophageal haemorrhages,[20] methylprednisolone and central nervous system haemorrhage and cerebrovascular accidents,[30] and milnacipran and migraine headaches.[41]

Among the seven other real signals as at 1 January 2002, five were not later confirmed by the literature during the 2002–11 period. These related to rivastigmine for gastric and oesophageal haemorrhages, pyridostigmine and ammonium chloride for migraine headaches, and lactulose and normegestrol for muscle pains. This absence of new evidence over a 10-year period suggests that these were likely to be false positive signals. Finally, the last two signals seem to be spurious and could also be considered as false positive. Coffee consumption has been consistently associated with reduced frequency of liver disease.[48] It is much likely that the association found between caffeine and hepatic enzymes and function abnormalities results from the fact that caffeine is included in fixed association with hepatotoxic drugs as paracetamol (acetaminophen) or ergot derivates. If paracetamol was concerned by the removal and should not be involved in this biased association, it could be related to cases connected to the use of other combinations including caffeine. Regarding the association found between levodopa in combination with a dopadecarboxylase inhibitor and muscle pain, it is likely that an indication bias occurred, as muscle pain can be encountered in the course of Parkinson disease.

One potential limitation for the application of the technique described here is that it is largely dependent on the list of drugs to select and remove reports from the database. Although this was established in collaboration with pharmacovigilance experts, it could certainly be improved. One way to standardize this would be to consider all drugs for which the studied event would constitute a type A reaction, making the list easy to update. However, if such a type of approach was considered for routine use in pharmacovigilance, as establishing these drug lists constitute a key aspect of the technique, a consensus approach involving a panel of experts on drug safety and experts in the clinical field of the considered event would be needed. In signal detection practice, it would somehow complete the standardization effort already done for the queries that should be used to identify the events and that led to the elaboration of the Standardized Medical Queries.

In this study, the identification of events was performed using MedDRA® HLTs. If this methodology was appropriate for research focussing on a potential drug competition bias for signal generation, other alternatives should be considered if the purpose of the signal generation was not research but pharmacovigilance regulatory monitoring of drug safety.

Another limitation concerns the methods used for the assessment of unmasked potential signals, which was performed to distinguish between already known signals, false positive signals and true positive signals. In this study, the evaluation of the consistency of the result with the existing literature was performed only for unmasked potential signals, which can be considered as a limit as it implies that assessors were not blinded of the existence of the association.

The unexpected result of this approach was that it led to the disappearance of signals for drugs that were not targeted by report removal. As this study was not designed to explore the effect of report removal for targeted drugs on the elimination of signals for other drugs, no conclusion can be drawn on this from the present results, and this effect needs to be further explored.

Conclusions

The results of the present study underline that the definition of the reference group is of great importance for signal generation. It can influence the detection thresholds and could increase the system sensitivity. In the present study, refining the reference group to minimize a potential competition bias led to unmasking a limited number of potential signals, of which some were later confirmed as true positives by the literature. The detection of these could have been made earlier using competition minimization methods such as that proposed herein.

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