

Research Paper

Aspirin- and Clopidogrel-associated Bleeding Complications: Data Mining of the Public Version of the FDA Adverse Event Reporting System, AERS

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Abstract

Objective: Adverse event reports (AERs) submitted to the US Food and Drug Administration (FDA) were reviewed to assess the bleeding complications induced by the administration of antiplatelets and to attempt to determine the rank-order of the association.

Methods: After a deletion of duplicated submissions and the revision of arbitrary drug names, AERs involving warfarin, aspirin, cilostazol, clopidogrel, ethyl icosapentate, limaprost alfadex, sarpogrelate, and ticlopidine were analyzed. Authorized pharmacovigilance tools were used for the quantitative detection of signals, i.e., drug-associated adverse events, including the proportional reporting ratio, the reporting odds ratio, the information component given by a Bayesian confidence propagation neural network, and the empirical Bayes geometric mean.

Results: Based on 22,017,956 co-occurrences, i.e., drug-adverse event pairs, found in 1,644,220 AERs from 2004 to 2009, 736 adverse events were listed as warfarin-associated adverse events, and 147 of the 736 were bleeding complications, including haemorrhage and haematoma. Both aspirin and clopidogrel were associated with haemorrhage, but the association was more noteworthy for clopidogrel. As for bleeding complications related to the gastrointestinal system, e.g., melaena and haematochezia, the statistical metrics suggested a stronger association for aspirin than clopidogrel. The total number of co-occurrences was not large enough to compare the association with bleeding complications for the other 5 antiplatelets.

Conclusions: The data strongly suggest the necessity of well-organized clinical studies with respect to antiplatelet-associated bleeding complications.

Key words: adverse events, AERS, warfarin, antiplatelets, pharmacovigilance.

Introduction

Arterial platelet-rich thrombosis differs from venous fibrin-rich thrombosis in terms of pathogenesis and prevention strategy, but both have considera-

ble medical impact [1, 2]. Myocardial infarction or stroke is often caused by arterial thrombosis, and venous thrombosis accounts for considerable mortality

from cardiovascular events [1, 2]. Antiplatelets are the basis for prevention of arterial thrombosis, whereas anticoagulants are effective for venous thrombosis; however, recent molecular investigations suggest the interdependence of platelets and the coagulation system in both forms of thrombosis [2], and physicians often recommend their combinations especially in patients with atrial fibrillation [3].

Currently, a myriad of patients are receiving combined warfarin-aspirin therapy to prevent thrombosis, but there is little clinical evidence of a therapeutic benefit compared with either alone, except for patients with acute coronary syndrome and mechanical heart valves [3-5]. The combination of warfarin and aspirin is more effective than aspirin alone for the prevention of recurrent cardiovascular events in patients with acute coronary syndrome [6, 7] and is more effective than warfarin alone for the prevention of thromboembolic events in patients with mechanical heart valves [8, 9]. On the other hand, there is compelling evidence that the warfarin-aspirin combination results in an increase in risk for serious bleeding complications [6-12]. Collectively, we should contemplate the risk-benefit balance of this combination, especially when data from randomized controlled trials are lacking [3-5].

Most reports on bleeding complications caused by anticoagulants and/or antiplatelets are of warfarin and/or aspirin, with little information available for other antiplatelets, e.g., cilostazol, clopidogrel, ethyl icosapentate, limaprost alfadex, sarpogrelate and ticlopidine. This study was conducted to assess the bleeding complications induced by the administration of antiplatelets and to attempt to determine the rank-order of the association, using more than a million case reports on adverse events (AERs) submitted to the US Food and Drug Administration (FDA). Authorized pharmacovigilance methods were used for quantitative signal detection [13-19], where a signal means a drug-associated adverse event or an association between a drug and an adverse event. Here, 7 antiplatelets were compared with warfarin in terms of susceptibility to bleeding complications.

Methods

Data sources

Input data for this study were taken from the public release of the FDA's Adverse Event Reporting System (AERS) database, which covers the period from the first quarter of 2004 through the end of 2009. The total number of reports used was 2,231,029. This database relies on reports of spontaneous adverse events by health professionals, consumers, and man-

ufacturers. The data structure of AERS is in compliance with international safety reporting guidance, ICH E2B, consisting of 7 data sets; patient demographic and administrative information (DEMO), drug/biologic information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), drug therapy start and end dates (THER), and indications for use/diagnosis (INDI). The adverse events in REAC are coded using preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Here, version 13.0 of MedDRA was used.

Prior to analysis, duplicated reports were deleted according to the FDA's recommendation of adopting the most recent CASE number, resulting in a reduction in the number of reports from 2,231,029 to 1,644,220. All drug names were unified into generic names by a text-mining approach, because AERS permits the registering of arbitrary drug names, including trade names and abbreviations. Spelling errors were detected by a spell checker software, GNU Aspell, and carefully confirmed by working pharmacists. The total number of errors was 223,239. Foods, beverages, treatments (e.g. X-ray radiation), and unspecified names (e.g. beta-blockers) were omitted for this study, and the total number of omissions was 164,384. A total of 22,017,956 co-occurrences were found in 1,644,220 reports, where a co-occurrence was a pair of a drug and an adverse drug event.

Definition of bleeding complications

The Standard MedDRA Queries (SMQs) are groupings of PT terms, which relate to defined medical conditions or areas of interest. A total of 82 SMQs have been released by the MedDRA maintenance and support services organization (<http://www.meddrasso.com/>). The heamorrhage SMQ consists of 421 PT terms; 91 heamorrhage laboratory PT terms (e.g., PT10022595: international normalised ratio (INR) increased, PT10022592: INR abnormal) and 330 heamorrhage PT terms (e.g., PT10055798: heamorrhage, PT10018852: haematoma). Here, 421 PT terms found in the heamorrhage SMQ were defined as bleeding complications.

Aspirin as antiplatelets

Aspirin is indicated for prevention of arterial thrombosis, but is also used to treat mild to moderate pain, fever and inflammatory diseases. Inclusion criteria for analysis included 1) "bayaspirin", "baby aspirin" or "children aspirin" for drug name, 2) term "low dose" in drug name, 3) PT terms located within a system organ class (SOC) of cardiac disorders (SOC10007541) or vascular disorders (SOC10047065),

4) PT terms located within a high level group term (HLGT) of vascular therapeutic procedures (HLGT10003184), 5) terms "stroke", "infarction", "thrombosis", "ischemia", "attack", "artery", "vascular" or "sclerosis" in PT terms, and 6) daily dose of 325mg or less.

Data mining

In pharmacovigilance analyses, data mining algorithms have been developed to identify drug-associated adverse events as signals that are reported more frequently than expected by estimating expected reporting frequencies on the basis of information on all drugs and all events in the database [17-19]. For example, the proportional reporting ratio (PRR) [13], the reporting odds ratio (ROR) [14], the information component (IC) [15], and the empirical Bayes geometric mean (EBGM) [16] are widely used, and indeed, the PRR is currently employed by the Medicines and Healthcare products Regulatory Agency (MHRA), UK, the ROR by the Netherlands Pharmacovigilance Centre, the IC by the World Health Organization (WHO), and the EBGM by the FDA.

All of these algorithms extract decision rules for signal detection and/or calculate scores to measure the associations between drugs and adverse events from a two-by-two frequency table of counts that involve the presence or absence of a particular drug and a particular event occurring in case reports. These algorithms, however, differ from one another in that the PRR and ROR are frequentist (non-Bayesian), whereas the IC and EBGM are Bayesian. In this section, only the scoring thresholds used in the present study are given, and the reader is referred to review articles for more extensive details of each statistical test [17-19].

Here, we define how a drug and associated adverse event is classified as a signal when using each statistical test. Using the PRR, a signal is detected if the count of co-occurrences is 3 or more and the PRR is 2 or more with an associated χ^2 value of 4 or more [13]. For the ROR, a signal is detected, if the lower bound of the 95% two-sided confidence interval exceeds 1 [14]. Signal detection using the IC is done using the IC025 metric, a criterion indicating the lower bound of the 95% two-sided confidence interval of the IC, and a signal is detected if the IC025 value exceeds 0 [15]. Finally, the EB05 metric, a lower one-sided 95% confidence limit of EBGM, is used and a signal is detected when EB05 is greater than or equal to the threshold value 2.0 [16]. In this study, the adverse events were listed as drug-associated, when at least 1 of 4 indices met the criteria indicated above.

Results

Table 1 lists the total number of co-occurrences, and the number of adverse events listed as drug-associated adverse events with co-occurrences. The total number of co-occurrences with warfarin was 156,357, and 59,855 for aspirin and 121,166 for clopidogrel, representing 0.710%, 0.272% and 0.550% of all co-occurrences in the database, respectively. In total, 736, 848 and 838 adverse events were listed as drug-associated adverse events with 64,289, 24,536, and 55,079 co-occurrences, respectively. The total number of co-occurrences was not large enough to compare the association with adverse events for cilostazol, ethyl icosapentate, limaprost alfadex, sargogrelate and ticlopidine.

Of 736 warfarin-associated adverse events, 147 were bleeding complications, the worst 20 being listed in Table 2. Based on the number of co-occurrences, the worst is an increase of INR, followed by heamorrhage, gastrointestinal heamorrhage, epistaxis, and a prolongation of prothrombin time in this order. Aspirin was also associated with these bleeding complications with exception of an abnormal INR. In the case of clopidogrel, exceptions included an increase of INR, a prolongation of prothrombin time, an abnormal INR and a prolongation of activated partial thromboplastin time (statistical data not shown).

Table 3 lists the statistical data on the association of warfarin, aspirin, and clopidogrel with heamorrhage and haematoma. The association with heamorrhage was more noteworthy for clopidogrel than aspirin, but the signals were weaker than for warfarin. A stronger signal for clopidogrel than aspirin was also observed for contusion (statistical data not shown).

Table 4 lists the data on melaena and haematochezia. The statistical metrics suggested a stronger association for aspirin than clopidogrel. This order was also found for gastrointestinal haemorrhage, a decrease of haematocrit value, cerebral haemorrhage, rectal haemorrhage, haemoptysis, subdural haematoma, haematemesis and gastric haemorrhage (statistical data not shown).

Discussion

The AERS database is considered a valuable tool; however, some limitations inherent to spontaneous reporting have been pointed out [17]. First, the data occasionally contain misspelling and miswords, although the structure of AERS is in compliance with the international safety reporting guidance. Second, the system was started more than 10 years ago, and reporting patterns have changed over time. Third, the

adverse events are coded using hierarchical terms of PTs of MedDRA, and changes in terminology over time also might affect the quality of the database. Last, there are a number of duplicate entries in the database. To overcome problems with data quality, we manually corrected mistakes in the data entities and deleted duplicates according to the FDA's recommended method. Previously, this system has been

used to assess adverse events accompanying the use of platinum agents [20], statins [21], 5-fluorouracil and capecitabine [22], tigecycline [23] and omeprazole and esomeprazole [24], and anticancer agent-associated hypersensitivity reactions [25, 26]. The reproducibility of clinical observations was suggested, but the number of co-occurrences should be large enough to detect a signal.

Table 1. Number of warfarin- and antiplatelet-associated adverse events.

	Co-occurrences in database ^{a)}	Adverse events ^{b)}	Co-occurrences with signal detected ^{b)}
warfarin	156,357	736	64,289
aspirin	59,855	848	24,536
cilostazol	8,410	459	3,337
clopidogrel	121,166	838	55,079
ethyl icosapentate	1,838	292	909
limaprost alfadex	1,052	227	521
sarpogrelate	1,081	223	540
ticlopidine	8,867	500	4,361

a) the total number of co-occurrences in the database.

b) the number of adverse events listed as drug-associated adverse events with co-occurrences.

Table 2. Worst 20 ranking bleeding complications reported for warfarin.

N	bleeding complications
4753	International normalised ratio increased
1072	Haemorrhage
1014	Gastrointestinal haemorrhage
724	Epistaxis
689	Prothrombin time prolonged
630	Contusion
595	International normalised ratio abnormal
526	Haematocrit decreased
522	Haematuria
494	Haematoma
489	Cerebral haemorrhage
468	Rectal haemorrhage
319	Melaena
312	Haemoptysis
283	Haemorrhage intracranial
268	Subdural haematoma
268	Haematemesis
254	Haematochezia
237	Activated partial thromboplastin time prolonged
184	Gastric haemorrhage

The total number of co-occurrences with warfarin was 156,357 in the AERS database. The adverse events were listed when at least 1 of 4 indices met the criteria, and 736 adverse events were listed as warfarin-associated adverse events with 64,289 co-occurrences in total. Among the 736 events, 147 were bleeding complications. The worst 20 were ranked according to the number of co-occurrences (N), with the official PT terms of MedDRA ver. 13.0.

Table 3. Signal detections for warfarin-, aspirin- and clopidogrel-associated haemorrhage and haematoma.

	N	PRR (χ^2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Haemorrhage					
Warfarin	1072	4.938* (3363.124)	5.080* (4.779, 5.381)	2.290* (2.202, 2.378)	4.902* (4.659)
Aspirin	209	2.506* (187.540)	2.517* (2.196, 2.837)	1.309* (1.112, 1.505)	2.455* (2.188)
Clopidogrel	541	3.208* (820.735)	3.247* (2.982, 3.513)	1.670* (1.547, 1.793)	3.170* (2.952)
Haematoma					
Warfarin	494	4.226* (1218.110)	4.326* (3.955, 4.697)	2.065* (1.936, 2.194)	4.186* (3.881)
Aspirin	118	2.634* (118.048)	2.646* (2.207, 3.084)	1.370* (1.109, 1.631)	2.542* (2.180)
Clopidogrel	254	2.801* (293.327)	2.829* (2.499, 3.159)	1.471* (1.292, 1.650)	2.750* (2.477)

N: the number of co-occurrences.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Haemorrhage and haematoma were coded as PT10055798 and PT10018852, respectively.

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean.

Table 4. Signal detections for warfarin-, aspirin- and clopidogrel-associated melaena and haematochezia.

	N	PRR (χ^2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Melaena					
Warfarin	319	3.019* (430.996)	3.064* (2.742, 3.385)	1.581* (1.421, 1.741)	2.972* (2.708)
Aspirin	334	8.288* (2126.968)	8.455* (7.583, 9.326)	3.011* (2.854, 3.168)	8.231* (7.516)
Clopidogrel	236	2.882* (289.243)	2.913* (2.561, 3.264)	1.511* (1.325, 1.696)	2.825* (2.535)
Haematochezia					
Warfarin	254	2.196* (165.111)	2.215* (1.956, 2.473)	1.124* (0.945, 1.303)	2.165 (1.951)
Aspirin	143	3.232* (218.231)	3.252* (2.757, 3.746)	1.663* (1.425, 1.900)	3.123* (2.712)
Clopidogrel	153	1.706 (44.202)	1.713* (1.461, 1.965)	0.759* (0.529, 0.988)	1.679 (1.468)

N: the number of co-occurrences.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Melaena and hematochezia were coded as PT10027141 and PT10018836, respectively.

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean.

In this study, a total of 736 adverse events were listed as warfarin-associated adverse events, and 147 of the 736 were bleeding complications. In 2007, Wysowski et al. reported the worst 30 ranking adverse events with use of warfarin using the AERS database from January 1993 to July 2006 [27]. Based on the number of reports, the adverse events ranked at a relatively high position included an increase of INR, drug interaction, gastrointestinal haemorrhage, haemorrhage, haematuria, anaemia, epistaxis, and melaena [27]. These adverse events also ranked at a higher position in this study, although the ranking was based on the number of occurrences and those without signals detected were excluded.

Both aspirin and clopidogrel were also associated with bleeding complications. The association with haemorrhage was more noteworthy for clopidogrel than aspirin; however, for gastrointestinal

bleeding complications, the statistical metrics suggested a stronger association for aspirin than clopidogrel. Recently, Hausen et al. reported the bleeding risk in patients with atrial fibrillation, treated with warfarin, aspirin, clopidogrel, and combinations thereof [10]. They performed a cohort study using the data in the Danish National Patient Registry, a system started in 1978, and employed the Cox model to estimate the risk of bleeding. Using warfarin monotherapy as a reference, the hazard ratio (95% confidential interval) for fatal bleeding was 1.37 (1.13-1.65) and 2.22 (1.30-3.77) for aspirin and clopidogrel monotherapy, respectively, but for gastrointestinal bleeding, it was 1.28 (1.17-1.41) and 1.18 (0.84-1.67), respectively. The data obtained in the present study does not conflict with the report by Hausen et al.

The incidence of bleeding with use of warfarin was variable among the clinical reports, and the vari-

ation might be explained by many factors, including definition of bleeding, patient mixes with indications and risks of bleeding, targeted INR, treatment protocol, treatment setting and length of follow-up [27]. The ARES database has an advantage in the use of well-organized authorized terms of MedDRA, although the incidence cannot be calculated in this analysis. Additionally, it should be noted that there is no credible counterfactual means, e.g., a randomized control group, to extract drug-associated adverse events as signals, and therefore disease-oriented adverse events can be listed as signals. The results can be biased by unmeasured confounding factors. Although the comparison of aspirin with clopidogrel possibly offsets them, a statistically well-organized methodology should be established to minimize their effects. In conclusion, the data strongly suggest the necessity of well-organized clinical studies with respect to antiplatelet-associated bleeding complications.

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Competing Interests

The authors have declared that no competing interest exists.

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