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Research Paper

Commonality of Drug-associated Adverse Events Detected by 4 Commonly Used Data Mining Algorithms

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Abstract

Objectives: Data mining algorithms have been developed for the quantitative detection of drug-associated adverse events (signals) from a large database on spontaneously reported adverse events. In the present study, the commonality of signals detected by 4 commonly used data mining algorithms was examined.

Methods: A total of 2,231,029 reports were retrieved from the public release of the US Food and Drug Administration Adverse Event Reporting System database between 2004 and 2009. The deletion of duplicated submissions and revision of arbitrary drug names resulted in a reduction in the number of reports to 1,644,220. Associations with adverse events were analyzed for 16 unrelated drugs, using the proportional reporting ratio (PRR), reporting odds ratio (ROR), information component (IC), and empirical Bayes geometric mean (EBGM).

Results: All EBGM-based signals were included in the PRR-based signals as well as IC- or ROR-based ones, and PRR- and IC-based signals were included in ROR-based ones. The PRR scores of PRR-based signals were significantly larger for 15 of 16 drugs when adverse events were also detected as signals by the EBGM method, as were the IC scores of IC-based signals for all drugs; however, no such effect was observed in the ROR scores of ROR-based signals.

Conclusions: The EBGM method was the most conservative among the 4 methods examined, which suggested its better suitability for pharmacoepidemiological studies. Further examinations should be performed on the reproducibility of clinical observations, especially for EBGM-based signals.

Key words: adverse event; Adverse Event Reporting System; FAERS; database; data mining; signal; signal detection; proportional reporting ratio; reporting odds ratio; information component; empirical Bayes geometric mean.

Introduction

The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS, formerly AERS) is a database that contains information on adverse event and medication error reports submitted to the FDA [1-3]. Besides those from manufacturers, reports can be submitted from health care professionals and the general public. The FAERS structure adheres to the International Safety Reporting Guidance issued by the International Conference on Harmonisation, ICH E2B, and adverse events are coded to terms in the

Medical Dictionary for Regulatory Activities (MedDRA) terminology [4]. The original system was initiated in 1969; however, reporting markedly increased following the last major revision in 1997 [5, 6]. To date, the FAERS contains more than 4 million reports and is the largest repository of spontaneously reported adverse events in the world [5, 6]. The FDA releases data to the general public, and this has allowed us to conduct pharmacoepidemiological studies and/or pharmacovigilance analyses.

Data mining algorithms have been developed for the quantitative detection of signals [7-11]. A signal indicates an association between a drug and an adverse event or drug-associated adverse event, including the proportional reporting ratio (PRR) [12], reporting odds ratio (ROR) [13], information component (IC) given by a Bayesian confidence propagation neural network [14], and empirical Bayes geometric mean (EBGM) [15]. Associations with adverse events of interests were previously analyzed for 16 drugs using reports in the FAERS database between 2004 and 2009 [16-22]. Whether an adverse event is detected as a signal has been shown to depend on the algorithms; however, of the 4 methods, the ROR method provided the highest number of signals, while the EBGM method provided the lowest [23]. In the present study, the commonality of PRR-, ROR-, IC-, and EBGM-based signals was examined.

Methods

Data were retrieved from the public release of the FAERS database from the first quarter of 2004 through to the end of 2009. The total number of reports obtained was 2,231,029. Duplicated reports were deleted and arbitrary drug names were revised, resulting in a reduction in the number of reports from 2,231,029 to 1,644,220. Signal scores, i.e., the PRR, ROR, IC, and EBGM values, were calculated for 16 unrelated drugs to assess associations with adverse events, including 2 antimicrobials (colistin and tigecycline), 4 HMG-CoA reductase inhibitors (statins) (pravastatin, simvastatin, atorvastatin, and rosuvastatin), 2 proton pump inhibitors (PPIs) (omeprazole and esomeprazole), warfarin, 2 antiplatelets (aspirin and clopidogrel), and 5 anticancer agents (cisplatin, carboplatin, oxaliplatin, 5-fluorouracil, and capecitabine). It is noted that the associations of these drugs with adverse events have already been published [16-22]. All values reported are the mean±standard deviation (SD). The unpaired Student's t-test/Welch's test or Mann-Whitney's U test was used for two-group comparisons of the values. P values of less than 0.05 were considered significant.

Results

Figure 1 shows the relationship among the PRR-, ROR-, IC-, and EBGM-based signals, which was commonly observed for all 16 drugs. All EBGM-based signals were included in the PRR-based signals as well as IC- or ROR-based ones. The PRR- and IC-based signals were included in the ROR-based ones. Therefore, ROR-based signals could be stratified into 5 groups; signals detected by the ROR only, signals detected by the ROR and PRR, signals detected by the ROR and IC, signals detected by the ROR, PRR, and IC, and signals detected by the 4 methods. Table 1 lists the numbers of signals in the 5 groups. The ratio of the total number of EBGM-based signals to that of signals detected by the ROR only varied from 3.9% with omeprazole to 57.3% with oxaliplatin. The ratio of the total number of EBGM-based signals to that of ROR-based signals varied from 1.7% with omeprazole to 20.5% with oxaliplatin.

Table 2 lists the PRR scores of PRR-based signals. Since PRR-based signals could be divided into 2 groups based on whether adverse events were also detected as signals by the EBGM method (Figure 1), the effects of additional detection by the EBGM method on PRR scores was examined. As shown in Table 2, the scores were significantly larger for 15 of 16 drugs when adverse events were also detected as signals by the EBGM method. Tables 3 and 4 show data on the ROR and IC, respectively. The effects of additional detection by the EBGM method found for PRR scores were not observed for the ROR, whereas the IC scores of IC-based signals were the same as the PRR scores of PRR-based signals.

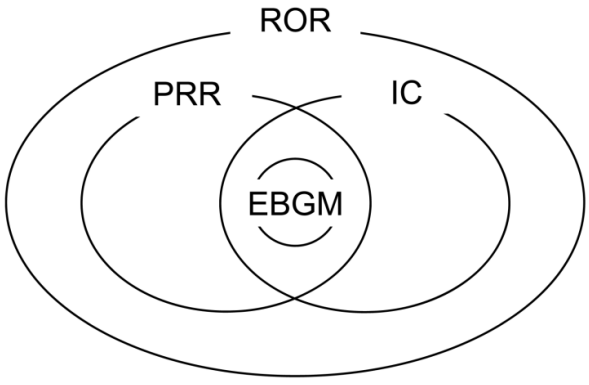

Figure 1. Commonality of signals detected by 4 commonly used data mining algorithms. PRR: proportional reporting ratio; ROR: reporting odds ratio; IC: information component; EBGM: empirical Bayes geometric mean. ROR-based signals were stratified into 5 groups; signals detected by the ROR only, signals detected by the ROR and PRR, signals detected by the ROR and IC, signals detected by the ROR, PRR, and IC, and signals detected by the 4 methods. The numbers of signals in the 5 groups are listed in Table 1.

Table 1. Numbers of signals in the 5 groups.

	ROR only	ROR&PRR	ROR&IC	ROR&PRR&IC	ROR&PRR&IC&EBGM
Cisplatin	356	98	49	206	175
Carboplatin	321	77	80	188	144
Oxaliplatin	262	64	60	196	150
Colistin	166	18	1	30	23
5-Fluorouracil	341	82	62	218	161
Capecitabine	340	67	51	198	146
Pravastatin	358	58	125	141	19
Simvastatin	284	61	268	101	30
Atorvastatin	304	65	295	164	55
Rosuvastatin	295	42	97	122	63
Tigecycline	155	18	2	29	44
Omeprazole	361	87	244	112	14
Esomeprazole	348	78	201	99	17
Warfarin	248	62	157	159	110
Aspirin	385	86	115	162	100
Clopidogrel	287	75	185	187	104

PRR: proportional reporting ratio; ROR: reporting odds ratio; IC: information component; EBGM: empirical Bayes geometric mean.
ROR-based signals were stratified into 5 groups; signals detected by the ROR only, signals detected by the ROR and PRR, signals detected by the ROR and IC, signals detected by the ROR, PRR, and IC, and signals detected by the 4 methods.

Table 2. PRR scores of PRR-based signals (the signals detected by the PRR method).

	All		Detected by EBGM		Not detected by EBGM		p
	N	PRR	N	PRR	N	PRR	
Cisplatin	479	8.03 ± 11.29	175	12.90 ± 16.73	304	5.23 ± 4.36	< 0.001
Carboplatin	409	6.80 ± 8.32	144	10.57 ± 12.25	265	4.76 ± 3.69	< 0.001
Oxaliplatin	410	7.72 ± 11.47	150	11.69 ± 17.16	260	5.43 ± 4.90	< 0.001
Colistin	71	29.30 ± 83.82	23	77.31 ± 136.92	48	6.29 ± 4.66	< 0.001
5-Fluorouracil	461	7.52 ± 10.03	161	11.61 ± 14.90	300	5.33 ± 4.72	< 0.001
Capecitabine	411	8.09 ± 13.06	146	12.07 ± 20.26	265	5.90 ± 5.09	< 0.001
Pravastatin	218	4.70 ± 4.26	19	10.48 ± 8.61	199	4.15 ± 3.11	< 0.001
Simvastatin	192	4.50 ± 4.81	30	8.99 ± 10.33	162	3.66 ± 1.94	< 0.001
Atorvastatin	284	3.76 ± 1.93	55	4.41 ± 1.99	229	3.61 ± 1.89	< 0.001
Rosuvastatin	227	5.20 ± 5.77	63	8.50 ± 9.37	164	3.94 ± 2.65	< 0.001
Tigecycline	91	37.88 ± 114.30	44	72.09 ± 158.16	47	5.85 ± 3.57	< 0.001
Omeprazole	213	4.69 ± 5.05	14	12.29 ± 15.28	199	4.16 ± 2.77	0.003
Esomeprazole	194	4.65 ± 3.83	17	7.19 ± 9.50	177	4.41 ± 2.68	0.513
Warfarin	331	5.28 ± 4.95	110	7.46 ± 7.38	221	4.19 ± 2.47	< 0.001
Aspirin	348	5.56 ± 4.93	100	8.05 ± 7.39	248	4.56 ± 2.96	< 0.001
Clopidogrel	366	4.85 ± 3.79	104	6.77 ± 5.44	262	4.08 ± 2.52	< 0.001

PRR-based signals were divided into 2 groups based on whether adverse events were also detected by the EBGM method.

Table 3. ROR scores of ROR-based signals (the signals detected by the ROR method).

	All		Detected by EBGM		Not detected by EBGM		p
	N	ROR	N	ROR	N	ROR	
Cisplatin	884	15.75 ± 34.12	175	13.92 ± 20.63	709	16.20 ± 36.69	0.002
Carboplatin	810	14.95 ± 43.93	144	11.07 ± 14.11	666	15.78 ± 47.96	0.001
Oxaliplatin	732	12.32 ± 31.94	150	12.41 ± 20.31	582	12.29 ± 34.32	< 0.001
Colistin	238	57.84 ± 165.03	23	78.97 ± 141.67	215	55.58 ± 167.47	0.028
5-Fluorouracil	864	14.89 ± 37.82	161	12.34 ± 18.38	703	15.47 ± 40.99	0.001
Capecitabine	802	17.16 ± 54.77	146	13.10 ± 25.20	656	18.06 ± 59.35	0.097
Pravastatin	701	10.00 ± 23.37	19	10.92 ± 9.30	682	9.97 ± 23.64	0.019
Simvastatin	744	5.37 ± 7.17	30	11.03 ± 16.14	714	5.13 ± 6.45	< 0.001
Atorvastatin	883	5.14 ± 8.66	55	4.61 ± 2.24	828	5.18 ± 8.92	< 0.001
Rosuvastatin	619	11.87 ± 27.18	63	8.93 ± 10.68	556	12.21 ± 28.44	0.074
Tigecycline	248	70.05 ± 381.27	44	74.82 ± 170.86	204	69.03 ± 413.14	0.008
Omeprazole	818	6.39 ± 11.04	14	16.92 ± 26.68	804	6.20 ± 10.51	0.003
Esomeprazole	743	6.83 ± 10.03	17	8.05 ± 11.77	726	6.80 ± 9.99	0.308
Warfarin	736	7.81 ± 13.74	110	8.36 ± 10.06	626	7.72 ± 14.30	< 0.001
Aspirin	848	11.86 ± 35.85	100	8.38 ± 8.38	748	12.32 ± 38.02	0.033
Clopidogrel	838	6.20 ± 9.01	104	7.19 ± 6.26	734	6.06 ± 9.33	< 0.001

ROR-based signals were divided into 2 groups based on whether adverse events were also detected by the EBGM method.

Table 4. IC scores of IC-based signals (the signals detected by the IC method).

	All		Detected by EBGM		Not detected by EBGM		p
	N	IC	N	IC	N	IC	
Cisplatin	430	1.64 ± 0.67	175	2.22 ± 0.55	255	1.24 ± 0.39	< 0.001
Carboplatin	412	1.51 ± 0.66	144	2.15 ± 0.53	268	1.16 ± 0.42	< 0.001
Oxaliplatin	406	1.60 ± 0.69	150	2.22 ± 0.62	256	1.23 ± 0.41	< 0.001
Colistin	54	1.82 ± 0.52	23	2.25 ± 0.47	31	1.51 ± 0.28	< 0.001
5-Fluorouracil	441	1.62 ± 0.70	161	2.32 ± 0.54	280	1.22 ± 0.40	< 0.001
Capecitabine	395	1.66 ± 0.70	146	2.31 ± 0.63	249	1.28 ± 0.41	< 0.001
Pravastatin	285	1.03 ± 0.48	19	1.98 ± 0.28	266	0.96 ± 0.41	< 0.001
Simvastatin	399	0.81 ± 0.50	30	1.96 ± 0.51	369	0.72 ± 0.36	< 0.001
Atorvastatin	514	0.92 ± 0.52	55	1.88 ± 0.41	459	0.80 ± 0.41	< 0.001
Rosuvastatin	282	1.27 ± 0.68	63	2.18 ± 0.60	219	1.00 ± 0.42	< 0.001
Tigecycline	75	2.05 ± 0.68	44	2.44 ± 0.58	31	1.50 ± 0.34	< 0.001
Omeprazole	370	0.80 ± 0.50	14	1.96 ± 0.44	356	0.75 ± 0.44	< 0.001
Esomeprazole	317	0.84 ± 0.48	17	1.78 ± 0.37	300	0.79 ± 0.43	< 0.001
Warfarin	426	1.28 ± 0.76	110	2.19 ± 0.71	316	0.97 ± 0.47	< 0.001
Aspirin	377	1.34 ± 0.68	100	2.18 ± 0.50	277	1.04 ± 0.45	< 0.001
Clopidogrel	476	1.20 ± 0.66	104	2.08 ± 0.56	372	0.95 ± 0.45	< 0.001

IC-based signals were divided into 2 groups based on whether adverse events were also detected by the EBGM method.

Discussion

Several studies previously compared data mining algorithms [13, 24-29]; however, as Bate and Evans recently concluded [7], different algorithms have slightly different properties such that one may consequently be preferable in a particular application. If used for pharmacovigilance, data mining algorithms should be assessed from the standpoint of early and timely signal detection [30-33]. Although few studies have published comparative data, Chen et al. recently compared the timing of early signal detection with PRR, ROR, IC, and EBGM using the FAERS database, and concluded that the ROR performed better [30]. We previously reported that the ROR method provided the highest number of signals, while the EBGM method provided the lowest [23]. The difference in the number of signals can be attributed to a higher rate of false positives or lower ability to detect signals. In the present study, the commonality of signals was clarified, as shown in Figure 1. The EBGM method was shown to be the most conservative among the 4 methods, which suggested that it was suitable for pharmacoepidemiological studies. In contrast, the ROR method was shown to be the most comprehensive, indicating its usefulness for pharmacovigilance. These results were consistent with the findings of Chen et al [30]. These 4 data mining algorithms were used in our previous studies [16-22], and adverse events were listed as drug-associated, when at least 1 of the 4 indices met the criteria. However, the results shown in Figure 1 demonstrated that lists of adverse events were only identical when the ROR method was applied, which suggested that care should be taken in interpreting data when signals are not detected by the EBGM method.

Based on the number of signals, 16 drugs could be classified into 4 groups. Group 1 included 2 antimicrobials, which were characterized by the lower number of signals. The total number of co-occurrences with colistin was only 1,491, and 1,906 for tigecycline. These were markedly less than those of the other 14 drugs; from 33,197 with oxaliplatin to 220,194 with atorvastatin. The lower number of signals can be explained by comparatively infrequent use, and, therefore, a smaller number of reports in the database. This is not related to the reliability of the signals.

Group 2 included 4 statins and 2 PPIs characterized by a lower number of EBGM-based signals, and group 3 included warfarin and 2 antiplatelets by a higher number of EBGM-based signals. Group 4 included 5 anticancer agents characterized by a much higher number of EBGM-based signals. The total number of ROR-based signals was similar among drugs in groups 2-4; from 619 with rosuvastatin to 884 with cisplatin. The ROR method is feasible for detecting more signals, including false positives, than the EBGM method. The difference observed in the ratio of EBGM-based to ROR-based signals may reflect whether adverse events are generally found.

A pilot study performed by Hochberg et al. in 2009 concerning drug-versus-drug comparisons revealed that the rank-order of adverse event rates in the FAERS database was consistent with the results of published studies [34], which encouraged the use of the database for comparisons. In other investigations, the number of reports with or without normalization by usage or sales during the corresponding period was used to compare drugs [35]; however, adverse events are underreported, which may lead to incorrect conclusions [36-38]. Signal scores have also been considered inappropriate for determining the rank-order of drugs in terms of risk; however, few studies have been published to date. In the present study, the EBGM method was shown to be the most conserva-

tive among the 4 methods; therefore, it is important to confirm whether this method can provide important information similar to that in well-organized clinical studies.

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Competing Interests

The authors have declared that no competing interest exists.

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