Pneumothorax as an Adverse Drug Event: An Exploratory Aggregate Analysis of the US FDA AERS Database Including a Confounding by Indication Analysis Inspired by Cornfield’s Condition

Manfred Hauben 1, 2, 3, 4, , Eric Y. Hung 1

1. Pfizer Inc (where work was performed)
2. New York University School of Medicine
3. New York Medical College
4. Brunel University

 Corresponding author: Manfred Hauben, Manfred.Hauben@Pfizer.com

© Ivyspring International Publisher. This is an open-access article distributed under the terms of the Creative Commons License (http://creativecommons.org/licenses/by-nc-nd/3.0/). Reproduction is permitted for personal, noncommercial use, provided that the article is in whole, unmodified, and properly cited.

Received: 2012.10.12; Accepted: 2013.03.13; Published: 2013.06.13

Abstract

Introduction: Pneumothorax is either primary or secondary. Secondary pneumothorax is usually due to trauma, including various non-pharmacologic iatrogenic triggers. Although not normally thought of as an adverse drug event (ADE) secondary pneumothorax is associated with numerous drugs, though it is often difficult to determine whether this association is causal in nature, or reflects an epiphenomenon of efficacy or inefficacy, or confounding by indication (CBI). Herein we explore this association in a large health authority drug safety surveillance database.

Methods: A quantitative pharmacovigilance (PhV) methodology known as disproportionality analysis was applied to the United States Food and Drug Administration (US FDA) Adverse Event Reporting System (AERS) database to explore the quantitative reporting dependencies between drugs and the adverse event pneumothorax as well the corresponding reporting dependencies between drugs and reported indications that may be risk factors for pneumothorax themselves in order to explore the potential contribution of CBI.

Results: We found 1. Multiple drugs are associated with pneumothorax; 2. Surfactants and oncology drugs account for most statistically distinctive associations with pneumothorax; 3. Pulmonary surfactants, pentamidine and nitric oxide have the largest statistical reporting associations; 4. CBI may play a prominent role in reports of drug-associated pneumothorax.

Conclusions: Disproportionality analysis (DA) can provide insights into the spontaneous reporting dependencies between drugs and pneumothorax. CBI assessment based on DA and Cornfield’s inequality presents an additional novel option for the initial exploration of potential safety signals in PhV.

Key words: Pneumothorax, disproportionality analysis

Introduction

Pneumothorax may be primary, in which no obvious trigger is identified, or secondary, which may be induced by trauma or iatrogenic factors. The iatrogenic factors typically cited include subclavian line placement, needle thoracentesis, and pleural biopsy.1 Another category of reported iatrogenic factors is drugs, although pneumothorax is probably not typically thought of as an adverse drug event (ADE).
The most commonly cited drugs in the published literature include oncology drugs, although other drugs, such as nitrous oxide, inhaled pentamidine and those associated with pulmonary fibrosis are also represented. The prominent association of oncology drugs with pneumothorax is intriguing and challenging to understand, as pneumothorax could theoretically be an epiphenomenon of drug efficacy (i.e. chemotherapy-induced lysis of sub-pleural tumor deposits) or inefficacy in this setting (i.e. progression of subpleural tumor deposits due to lack of efficacy). Confounding by indication (CBI) is therefore an important consideration, given that pneumothorax may reflect the natural history/complications of malignancy. There is variation in the use of the term CBI but for our purposes CBI means that the treatment indication is independently associated with the ADE. It is difficult to exclude one of the aforementioned possibilities. Further complicating these associations are the co-occurrence of cancers and pneumothorax as part of a syndromic phenotype, such as the association of renal cell carcinoma and pneumothorax as elements of Birt-Hogg-Dube syndrome.

Most of the published literature on pneumothorax consists of case reports. As pharmacovigilance (PhV) specialists we routinely access and analyze rich sources of ADEs such as large spontaneous reporting systems (SRS) maintained by health authorities. We were curious to discover and better understand the representation of pneumothorax as an ADE in these data sets.

Herein we present an analysis of the data of pneumothorax as a reported ADE in a large health authority post-approval drug safety database. The primary objective is to increase scientific understanding of this spontaneous reporting association. A secondary objective is to present an adaptation of an “old” epidemiological concept, Cornfield’s inequality, that is novel for the application domain of PhV to explore the potential role of CBI in the association of pneumothorax for a subset of drugs for which this is an especially apt consideration. This could support real-world PhV because when drug-event combinations of interest are initially identified that could represent a signal of a novel association, an analyst will typically perform a first pass qualitative triage based on scientific judgment that includes consideration of CBI. A CBI analysis of this sort therefore has the potential to provide quantitative decision support for first pass triage in PhV.

Methodology

1. Databases

The data set analyzed was the United States Food and Drug Administration (US FDA) Adverse Event Reporting System (AERS) database. AERS is a spontaneous reporting system (SRS) database for post-approval safety surveillance that serves as an early warning system for ADEs not detected in pre-approval testing. The AERS database was analyzed from January 1st, 1969 through December 31st, 2010. The data was preprocessed to reduce redundant drug nomenclature and duplicate reports. Suspected adverse drug reactions are coded with hierarchical medical thesaurus known as the Medical Dictionary for Regulatory Activities (MedDRA). The hierarchy maps the verbatim reported term to a Lower level Term (LLT) and then to a Preferred Term (PT) in the hierarchy, that is intended to capture a given medical concept in a standardized manner.

2. Statistical Analysis Methodology

We performed two-dimensional (2-D) disproportionality analysis (DA) limited to suspect drugs. DA calculates the number of reports, proportionate representation, or odds of a given 2-D drug-event combination (DEC), that would be expected based on chance spontaneous reporting and recording of the corresponding drug(s) and event(s) in the database. In combination with the number of reports actually observed, an observed-to-expected ratio of reporting frequencies, ratios or odds is calculated (O/E). There are variations in the specific implementation of DA with SRS data including frequentist and Bayesian formulations. No single method has been proven to be the method-of-choice. Details on DA may be found in the published literature.

We used a form of DA known as the multi-item gamma-Poisson shrinker (MGPS) (Oracle, Redwood Shores, CA) for this analysis. This algorithm models reporting frequencies as realizations of a Poisson process in which the Poisson parameter is itself considered a random variable whose distribution is a mixture of two gamma distributions. The initial parameters of the gamma mixture are determined using a negative binomial maximum likelihood algorithm to determine the prior probabilities of different possible O/E ratios. Prior probabilities are updated based on the number of reports of the DEC of interest using Baye’s rule. In effect this calculates each O/E ratio as a composite of the grand mean O/E of all reported DECs, which is close to one (Hauben M, unpublished data) and that of the combination of interest, with the weighting for each determined by the O and E counts. When one or both of these counts are low the grand mean is heavily weighted but as information is gained, the individual combination’s O/E is weighed more heavily and may eventually dominate the calculation.
The O/E metric calculated is the empirical Bayes geometric mean (EBGM) and its associated 90% posterior interval (PI) defined by the lower 5th (EB05) and upper 95th (EB95) percentiles of the EBGM. An EB05>2 was used to define an interestingly large O/E, also known as a ‘signal of disproportionate reporting (SDR).’ Calculations were performed at the MedDRA PT level. Basic covariate stratification by age, gender and year of report was performed to mitigate the effects of confounding by these variables and calculate a summary Mantel-Haenszel type O/E ratio.

We also performed the calculation for drug-indication pairs. This was inspired by Cornfield’s inequality that in order for an effect with a relative risk (RR) of some magnitude X to be fully explainable by a confounding factor, a necessary condition is that factor would have to be X times more common in exposed versus unexposed persons.

For each drug with an SDR for the ADE PT (PT ADE) pneumothorax we reviewed the reported drug-indications to identify the most significant confounders for this event based on current clinical knowledge. From the latter indications for each drug, we searched for those that were prominently represented based on the number of reports (and therefore representative indications for that drug) and that were likely to be quantitatively most influential on our calculations based on higher EBGMs. If more than one likely candidate confounding indication was identified all were considered and included in the outputs.

Reporting of indications may be inherently different than reporting of events since the former are not necessary to create an ADE report but the latter are a required minimum data element, and because reporting of indications may be more deterministic and less stochastic than events. That is, the drug is nonrandomly selected for specific indications whereas many ADEs are typically the result of multiple random and nonrandom factors. Therefore the range of ADEs reported with a drug is expected to be much wider than the range of reported indications. We therefore introduced an adjustment based on the reduced range of unique indication PTs (PTs IND) recorded in the database relative to the range of unique PTs ADE, both overall in the database and preferentially for specific drugs. Expressed a little differently the number of unique reported indications in the entire database is less than the number of unique reported ADEs in the entire database and all else being equal, the difference between reported indications and reported ADEs may be larger or smaller for specific drugs depending on the overall safety profile and the number of treatment indications. The idea is to give a “more severe” test, (e.g. part of a best case-worst case scenario) for whether CBI is quantitatively plausible within the set of ADE reports. We calculated the number of unique PTs ADE and PTs IND for the overall database and for the specific subset of drugs with statistically significant reporting relationship. The ratio of these two in the overall database may be viewed as an adjustment for expected indication counts, and that for specific drugs as an adjustment for observed indication counts. Expressed a little differently we isolated the component of observed and expected counts for indication related to the distribution of counts within the reduced range of PTs IND for each drug. The adjusted CBI index (ACBII) was therefore calculated as follows:

\[
\text{ACBII} = \frac{\text{UCBII}}{\left(\frac{Y}{X}\right)}
\]

Where adjusted (O/E) IND = \(\frac{O_{\text{IND}}}{Y}\)/\(\frac{E_{\text{IND}}}{X}\)

The more the ACBII’s metric exceeds one the more it suggest that the restriction of the reported indications to confounding indications is substantial relative to the magnitude of the SDR. We thus are comparing SDRs for drug-ADE pairs and drug-indications pairs, which we denote by SDR ADE and SDR IND.

**Results**

There were 878 unique reported suspect drugs, (either single drugs or combination products) in 3681 reports recording pneumothorax as an ADE (17% of 5043 total drugs in the database). The 3681 reports of the ADE pneumothorax represents 0.08% of 4637278 total ADE reports in the database. The number of reports per drug ranged from 1 to a maximum of 115. The majority (821/878 or 93%) of drugs associated with pneumothorax had only a single report compared to 848392/1766279 (48%) of all DECs with only one report.

Fifty-one of the 878 (5.8%) drugs in AERS listing pneumothorax were associated with an SDR (Table 1).
| Generic Name                  | PT<sub>ADE</sub>       | N | EB05 | EBGM | EB95 |
|------------------------------|------------------------|---|------|------|------|
| Colfosceril                  | Pneumothorax           | 9 | 84.1 | 152.2| 258.4|
| Poractant Alfa               | Pneumothorax           | 9 | 34.3 | 62.0 | 105.3|
| Beractant                    | Pneumothorax           | 11| 35.3 | 60.1 | 97.1 |
| Nitric Oxide                 | Pneumothorax           | 19| 9.77 | 16.4 | 24.4 |
| Pentamidine                  | Pneumothorax           | 11| 5.58 | 14.3 | 27.4 |
| Alglucosidase Alfa           | Pneumothorax           | 18| 5.3  | 9.06 | 15.8 |
| Carmustine                   | Pneumothorax           | 15| 4.75 | 8.52 | 16.2 |
| Dacarbazine                  | Pneumothorax           | 13| 4.18 | 7.57 | 15.3 |
| Bleomycin                    | Pneumothorax           | 22| 4.46 | 6.52 | 9.59 |
| Gefitinib                    | Pneumothorax           | 32| 4.75 | 6.45 | 8.7  |
| Docetaxel                    | Pneumothorax           | 86| 5.25 | 6.3  | 7.51 |
| Bevacizumab                  | Pneumothorax           | 104| 4.76| 5.6  | 6.57 |
| Vinblastine                  | Pneumothorax           | 13 | 3.29 | 5.35 | 8.58 |
| Epoprostenol                 | Pneumothorax           | 13 | 3.06 | 4.94 | 7.74 |
| Actinomycin-D                | Pneumothorax           | 10 | 2.83 | 4.92 | 8.39 |
| Carboplatin                  | Pneumothorax           | 80 | 4.05 | 4.89 | 5.85 |
| Dornase Alfa                 | Pneumothorax           | 6  | 2.16 | 4.56 | 10.9 |
| Gemcitabine                  | Pneumothorax           | 70 | 3.69 | 4.51 | 5.46 |
| Leflunomide                  | Pneumothorax           | 31 | 3.27 | 4.42 | 5.88 |
| Etoposide                    | Pneumothorax           | 52 | 3.47 | 4.38 | 5.47 |
| Paclitaxel                   | Pneumothorax           | 81 | 3.57 | 4.3  | 5.14 |
| Ifosfamide                   | Pneumothorax           | 18 | 2.78 | 4.14 | 6    |
| Vinorelbine                  | Pneumothorax           | 21 | 2.82 | 4.08 | 5.75 |
| Everolimus                   | Pneumothorax           | 22 | 2.75 | 3.94 | 5.51 |
| Pamidronic Acid              | Pneumothorax           | 23 | 2.76 | 3.92 | 5.44 |
| Erlotinib                    | Pneumothorax           | 24 | 2.75 | 3.88 | 5.35 |
| Doxorubicin                  | Pneumothorax           | 61 | 3.04 | 3.76 | 4.62 |
| Mycophenolic Acid Slow Release| Pneumothorax          | 8  | 2.04 | 3.72 | 6.39 |
| Vincristine                  | Pneumothorax           | 55 | 2.85 | 3.58 | 4.44 |
| Ambrisentan                  | Pneumothorax           | 19 | 2.42 | 3.57 | 5.11 |
| Methylprednisolone           | Pneumothorax           | 40 | 2.57 | 3.35 | 4.31 |
| Hydrocortisone               | Pneumothorax           | 13 | 2.09 | 3.34 | 5.12 |
| Prednisolone                 | Pneumothorax           | 45 | 2.5  | 3.2  | 4.06 |
| Amiodarone                   | Pneumothorax           | 40 | 2.46 | 3.2  | 4.12 |
| Methotrexate                 | Pneumothorax           | 75 | 2.64 | 3.2  | 3.85 |
| Trastuzumab                  | Pneumothorax           | 16 | 2.09 | 3.18 | 4.69 |
| Melphalan                    | Pneumothorax           | 17 | 2.11 | 3.18 | 4.64 |
| Dexamethasone                | Pneumothorax           | 40 | 2.44 | 3.18 | 4.09 |
| Midazolam                    | Pneumothorax           | 18 | 2.14 | 3.18 | 4.59 |
| Bosentan                     | Pneumothorax           | 28 | 2.3  | 3.16 | 4.26 |
| Cisplatin                    | Pneumothorax           | 59 | 2.5  | 3.11 | 3.83 |
| Pemetrexed                   | Pneumothorax           | 19 | 2.09 | 3.08 | 4.41 |
| Heparin                      | Pneumothorax           | 47 | 2.37 | 3.03 | 3.82 |
| Azathioprine                 | Pneumothorax           | 21 | 2.07 | 2.99 | 4.2  |
| Sunitinib                    | Pneumothorax           | 34 | 2.24 | 2.99 | 3.92 |
| Botulinum Toxin Type A       | Pneumothorax           | 23 | 2.06 | 2.93 | 4.07 |
| Tacrolimus                   | Pneumothorax           | 41 | 2.24 | 2.91 | 3.73 |
| Propofol                     | Pneumothorax           | 21 | 2  | 2.89 | 4.07 |
| Cyclophosphamide             | Pneumothorax           | 62 | 2.29 | 2.83 | 3.47 |
| Palivizumab                  | Pneumothorax           | 27 | 2.04 | 2.82 | 3.82 |
| Oxaliplatin                  | Pneumothorax           | 30 | 2.03 | 2.76 | 3.68 |
The statistical reporting dependencies or SDRs (e.g., O/E reporting that exceeds chance expectation), expressed in the EBGM, ranged from 2.76 to a maximum of 152.2. Six non-oncology drugs accounted for the strongest statistical reporting associations. Pulmonary surfactants accounted for three of these (152.2 for colfosceril, 62.0 for poractant alpha, and 60.1 for beractant), followed by nitric oxide (16.4), pentamidine (14.3) and alglucosidase alpha (9.06). The highest values involving pulmonary surfactants illustrate the potential for CBI through various reporting mechanisms in SRS databases, as these compounds have been documented to actually decrease the incidence of pneumothorax in clinical trials. Twenty-six oncology drugs were associated with an SDR ADE. The EBGMs for these drugs ranged from 2.76 for oxaliplatin to 8.52 for carmustine.

The CBI analysis (Table 2) is notable for a wide range of UCBIIIs with all drug-specific values >1, and two drugs, carmustine and docetaxel, with an ACBII consistently <1. Among the six strongest drug-ADE associations described above, there are potentially confounding indications with significant statistical associations (SDRIND) with each drug that are large relative to the magnitude of the SDR ADE as reflected in large UCBII and/or ACBIIs greater than one for beractant, nitric oxide, pentamidine, and poractant alpha. The most obvious of these, as discussed qualitatively above, is neonatal respiratory distress syndrome for the pulmonary surfactants beractant and proractant alpha (the precise indications were not recorded in colfoscierl reports), which, as stated above, have been shown in clinical trials to decrease the risk of pneumothorax in this condition. Pentamidine was notable for a very high ACBII (13.79) consistent with clinicopathological correlates of pneumocystis tissue invasion, inflammation, and necrosis. Similarly nitric oxide is used to treat pulmonary hypertension in neonates with pneumothorax and in both of the latter clinical scenarios maximal ventilation may be employed which may cause air leaks.

For the oncology drugs, various carcinomas, sarcomas and lymphomas were potentially confounding indications associated with strong statistical associations with the drug. Carmustine and docetaxel have the largest and fifth largest EBGM among oncology drugs and were the two oncology drugs associated with an ACBII <1 for the single identified confounding indication for each drug. Of note carmustine is the drug with the most established association with pneumothorax based on the occurrence of upper lobe fibrobullos disease. Docetaxel is the one drug for which we were able to identify a case report involving multiple positive rechallenges with each multidrug chemotherapy course. However bleomycin, another oncology agent with an established reputation for pulmonary toxicity that could provide a mechanistic context for pneumothorax, had the second largest EBGM and was associated with one of the highest ACBI.

### Table 2. Analysis of Spontaneous Reporting Pneumothorax

| Drug                | PT$_{ADE}$: Pneumothorax | Confounding Indication* | PT$_{ADE}$/PT$_{IND}$ | O(E)$_{IND}$/ (O/E)$_{ADE}$ |
|---------------------|---------------------------|-------------------------|------------------------|-----------------------------|
| **Actinomycin-D**   | 10                        | 2.83                    | 4.92                   |                             |
|                     | N                         | 56                      | 243.3                  |                             |
|                     | EBS                      | 148                     | 124.3                  |                             |
|                     | EBGM                     | 304.9                   | 142.6                  |                             |
|                     | PT$_{IND}$               | 829/85                  | 9.75                   | 61.97                       |
|                     |                          |                         |                        | 11.06                       |
| **Alglucosidase alpha** | 18.3                    | 5.03                    | 9.06                   |                             |
|                     | N                         | 19                      |                         |                             |
|                     | EBS                      | 19                      |                         |                             |
|                     | EBGM                     | 19                      |                         |                             |
|                     | PT$_{IND}$               | NA                      |                         |                             |
|                     |                          | NA                      |                         |                             |
| **Ambrisentan**     | 19                        | 2.42                    | 3.57                   |                             |
|                     | N                         | 19                      |                         |                             |
|                     | EBS                      | 19                      |                         |                             |
|                     | EBGM                     | 19                      |                         |                             |
|                     | PT$_{IND}$               | NA                      |                         |                             |
|                     |                          | NA                      |                         |                             |
| **Azathioprine**    | 21                        | 2.07                    | 2.99                   |                             |
|                     | N                         | 21                      |                         |                             |
|                     | EBS                      | 21                      |                         |                             |
|                     | EBGM                     | 21                      |                         |                             |
|                     | PT$_{IND}$               | NA                      |                         |                             |
|                     |                          | NA                      |                         |                             |
| **Beractant**       | 11                        | 35.3                    | 60.1                   |                             |
|                     | N                         | 8                       |                         |                             |
|                     | EBS                      | 8                       |                         |                             |
|                     | EBGM                     | 297.3                   |                         |                             |
|                     | PT$_{IND}$               | 560.3                   |                         |                             |
|                     |                          | 115/11                  |                         |                             |
|                     |                          | 10.45                   |                         |                             |
|                     |                          | 9.32                    |                         |                             |
|                     |                          | 1.55                    |                         |                             |
| **Bevacizumab**     | 104                       | 4.76                    | 5.6                    |                             |
|                     | N                         | 1319                    | 64.8                   |                             |
|                     | EBS                      | 1319                    | 67.8                   |                             |
|                     | EBGM                     | 3083/467                | 6.60                   |                             |
|                     | PT$_{IND}$               | 1193                    | 17                     |                             |
|                     |                          | 17.8                    |                         |                             |
|                     |                          | 3.18                    |                         |                             |
|                     |                          | 0.84                    |                         |                             |
| **Bleomycin**       | 22                        | 4.46                    | 6.523                  |                             |
|                     | N                         | 511                     | 345.1                  |                             |
|                     | EBS                      | 511                     | 371.3                  |                             |
|                     | EBGM                     | 1386/180                | 7.70                   |                             |
|                     | PT$_{IND}$               | 150                     | 344.3                  |                             |
|                     |                          | 394.6                   |                         |                             |
|                     |                          | 60.50                   |                         |                             |
|                     |                          | 13.67                   |                         |                             |
| **Carboplatin**     | 80                        | 4.05                    | 4.89                   |                             |
|                     | N                         | 2278                    | 43.6                   |                             |
|                     | EBS                      | 2278                    | 45.2                   |                             |
|                     | EBGM                     | 3143/539                | 5.83                   |                             |
|                     | PT$_{IND}$               | 690                     | 30.5                   |                             |
|                     |                          | 32.4                    |                         |                             |
|                     |                          | 6.63                    |                         |                             |
|                     |                          | 1.98                    |                         |                             |
| **Carmustine**      | 15                        | 4.75                    | 8.52                   |                             |
|                     | N                         | 55                      | 29.5                   |                             |
|                     | EBS                      | 55                      | 37                     |                             |
|                     | EBGM                     | 1052/119                | 8.84                   |                             |
|                     | PT$_{IND}$               | 25                      |                         |                             |
|                     |                          |                         | 4.34                   |                             |
|                     |                          |                         | 0.85                   |                             |

http://www.medsci.org
| Drug          | PT ADE: Pneumothorax | Confounding Indication* | PTs IND | PTs ADE/PTs IND | (O/E)IND / (O/E)ADE |
|---------------|----------------------|-------------------------|---------|-----------------|---------------------|
| Cisplatin     | 59                   | 2.5                     | 3.11    | 414             | 15005/8646          |
|               |                      | Sm cell lung cancer     |         |                 |                     |
|               |                      | stage unspec            |         |                 |                     |
|               |                      | Oesophageal carcinoma   |         |                 |                     |
|               |                      | Non-small cell lung     |         |                 |                     |
| Colfosceril   | 9                    | 84.1                    | 152.2   | NA**            |                     |
|               |                      | NA                      | NA      | NA              |                     |
|               |                      | NA                      | NA      | NA              |                     |
| Cyclphosphamide| 62                  | 2.29                    | 2.83    | 2667            |                     |
|               |                      | Breast cancer           |         |                 |                     |
| Dacarbazine   | 13                   | 4.18                    | 7.57    | 87              |                     |
|               |                      | Metastatic malignant    |         |                 |                     |
|               |                      | melanoma                |         |                 |                     |
| Docetaxel     | 86                   | 5.25                    | 6.3     | 868             |                     |
|               |                      | Non-small cell lung     |         |                 |                     |
|               |                      | cancer                  |         |                 |                     |
| Doxorubicin   | 61                   | 3.04                    | 3.76    | 1597            |                     |
|               |                      | Breast cancer           |         |                 |                     |
| Erlotinib     | 24                   | 2.75                    | 3.88    | 687             |                     |
|               |                      | Lung neoplasm malignant |         |                 |                     |
|               |                      | Non-small cell lung     |         |                 |                     |
| Etoptoside    | 52                   | 3.47                    | 4.38    | 476             |                     |
|               |                      | Sm cell lung cancer     |         |                 |                     |
|               |                      | stage unspec            |         |                 |                     |
| Gefitinib     | 32                   | 4.75                    | 6.45    | 453             |                     |
|               |                      | Lung adenocarcinoma     |         |                 |                     |
| Gemcitabine   | 70                   | 3.69                    | 4.51    | 1621            |                     |
|               |                      | Non-small cell lung     |         |                 |                     |
| Ifosfamide    | 18                   | 2.78                    | 4.14    | 135             |                     |
|               |                      | Sarcoma                 |         |                 |                     |
| Oxaliplatin   | 30                   | 2.03                    | 2.76    | 1426            |                     |
|               |                      | Colon cancer            |         |                 |                     |
|               |                      | Colorectal cancer       |         |                 |                     |
| Melphalan     | 17                   | 2.11                    | 3.18    | NA              |                     |
| Methotrexate  | 75                   | 2.64                    | 3.2     | NA              |                     |
| Nitric Oxide  | 19                   | 9.8                     | 16.4    | 49              |                     |
| Paclitaxel    | 81                   | 3.57                    | 4.3     | 1598            |                     |
| Pemetrexed    | 19                   | 2.09                    | 3.08    | NA              |                     |
| Pentamidine   | 11                   | 5.6                     | 14.3    | NA              |                     |
|               |                      | Pneumocystis jiroveci   |         |                 |                     |
|               |                      | pneumonia               |         |                 |                     |
| Poractant Alfa| 9                    | 34.3                    | 62      | 26              |                     |
|               |                      | Neonatal resp distress  |         |                 |                     |
|               |                      | syndrome                |         |                 |                     |
| Sunitinib     | 34                   | 2.24                    | 2.99    | 2170            |                     |
|               |                      | Metastatic renal cell   |         |                 |                     |
|               |                      | carcinoma               |         |                 |                     |
| Trastuzumab   | 16                   | 2.09                    | 3.18    | 2546            |                     |
|               |                      | Breast cancer metastatic|         |                 |                     |
| Vinblastine   | 13                   | 3.29                    | 5.35    | 385             |                     |
| Vincristine   | 55                   | 2.85                    | 3.58    | 1009            |                     |
| Vinorelbine   | 21                   | 2.82                    | 4.08    | 677             |                     |

The overall ratio of PT ADE/PT IND in the database is 15005/8646 = 1.73

**Note:** NA** indicates no obvious confounding indications identified in any reports.

**Specific indications not reported.**
Discussion

We found a significant number of ADE reports of pneumothorax in a large health authority SRS database though it was rare as a proportion of all reports. Most drugs with SDRs were oncology drugs of various mechanisms of action but the strongest statistical associations involved a small number of non-oncology drugs, namely pulmonary surfactants and pentamidine, that our analysis supports as CBI. The results are consistent with pulmonary surfactants’ reported reduction in the incidence of pneumothorax in neonatal respiratory distress syndrome, and clinical-pathological correlates indicating that pneumothorax in the setting of pneumocystis pneumonia may reflect peripheral microbial inflammation, invasion and tissue necrosis corresponding to gradients in aerosol particle deposition.14-17 Of note ACBIIIs for the surfactant preparations for which indication was reported were all greater than one and for pentamidine was 13.79. The two oncology drugs with a consistent finding of an ACBII <1 seem to have the most persuasive association with pneumothorax from independent datasets. Therefore this approach to CBI analysis showed preliminary hints of utility for initial exploratory analysis to provide quantitative support for initial understanding and triage of SDRs in PhV. The absence of obvious confounding indications does not necessarily rule out CBI as a causal or contributory factor. In some instances the absence of an obvious recorded indication was due to the fact that the indication was not reported in any reports (i.e. colfosceril). In other instances the reported indication could have been a confounding factor, though not as well established as in the classic examples of various oncology drugs. For instance the reported indication for alglucosidase alpha was glycogen storage disease type II, which involves serious pulmonary disease that could at least theoretically be associated with pneumothorax via natural history or iatrogenic disease.35

There are significant limitations to our analysis most notably the usual ‘warnings, precautions and indications for use’ for SRS data which precludes making causal inferences except in unusual circumstances24 which are amplified by the aforementioned differences in event versus indication reporting. We did not perform a case-level clinical review (case narratives are not included in AERS extracts for public use) and results of any quantitative analysis of SRS data is most meaningful when correlated with case-level clinical information. DA is based on 2x2 contingency tables methods and therefore do not accommodate the complex multivariate drug and event relationships that are characteristic of such data and which may be especially pertinent to the oncology setting where multi-drug treatment protocols are common. For example, the pulmonary toxicity of docetaxel has been reported to be enhanced by co-administered gemcitabine.36,37 Finally like any observational database, and perhaps especially so for SRS data, there are other reporting artifacts such as unrecorded confounding and effect modification which this approach does not address and which typically remain unresolved in initial signal detection in PhV.

The application of even basic disproportionality analysis has been the subject of heated debate with extreme viewpoints of “unbridled optimism” to “considerable skepticism”.38 In other words some authorities consider such analysis a “garbage in garbage out” exercise of no value and potential harm, while others unrealistically maintain that such quantitative analysis, if performed with certain proprietary software, can neutralize the enormous limitations of spontaneous reports. We take a moderate position between the aforementioned extremes. With our analysis, which went beyond the usual drug-ADE analysis to include a drug-indication analysis, so one must be even more cautious in interpretation.

While the above limitations are substantial and clearly disqualifies this approach for making inferences, it is does not necessarily disqualify its judicious application as an exploratory analysis tool to help refine an initial index of suspicion related to CBI. Quoting an author writing about another exploratory analysis tool39 “data mining and fishing expeditions are dirty words, but tempered with an awareness of the fallacies they can lead to, and supported by honest documentation, it is not a scientific crime” to use them in this context to search for a possible contribution of CBI to the reporting association between the drug and the event.

An analysis using Cornfield’s inequality in this setting has advantages including the fact that it is simply an extension of the same basic calculation used for the drug-ADE pair to drug-indication pairs and thus easily implementable for front-end signal detection in PhV, as well as being transparent and intuitive but there are other alternative approaches including calculating O/E ratios within different levels of a confounding variable and/or calculating an adjusted summary measure as with Mantel-Haenszel methods (as we did with age, gender and reporting year). Another approach applied to SRS data is to perform the DA on a subset of drugs within a pharmacological/therapeutic class or for specific indication(s).40-48 Although this has been performed at times there are
limitations to these approaches as well. For example depending on the specific implementation of the DA such an approach can potentially mask credible associations if they exist with multiple drugs within the pharmacological/therapeutic class. Utilizing the generality of the database as a background may provide a better picture of the statistical reporting associations in the universe of drugs, rather than just differences between drugs within a subset of drugs. This may inevitably entail a trade-off between sensitivity and specificity. Finally such an approach allows analysis of only one drug class per analysis.

Finally our adjustment, while based on plausibility considerations, is still essentially somewhat ad hoc, (as are many exploratory analysis in PhV) but it provides a starting point for further discussion and research including a systematic assessment of its operating characteristics, as well as that of other potential adjustment factors. It would also be interesting to perform a systematic study to establish operating characteristics of U/ACBII that could potentially identify optimum thresholds that might obviate the need for correction.

Acknowledgements

Manfred Hauben was responsible for the initiation and design of the study as well as manuscript writing and editing. Eric Hung was responsible for the data generation and review and editing of the manuscript. Both authors take responsibility for the manuscript content.

Competing Interests

Manfred Hauben is a full time employee of Pfizer Inc which manufactures/markets drugs discussed in this article and/or competing drugs from the same pharmacological/therapeutic class as those discussed in this article and owns stock and stock options in other pharmaceutical companies that may manufacture drugs included in this study and/or other drugs within the same pharmacological/therapeutic classes.

Eric Hung is a full time employee of Pfizer Inc and owns stock and stock options in Pfizer Inc.

References

1. Sahn S, Heffner JE. Spontaneous pneumothorax. NEJM 2000; 342(12): 868-874.
2. Wilson KS, Brigden ML, Alexander S et al. Fatal pneumothorax in “BCNU Lung”. Medical and Pediatric Oncology 1982; 10: 195-99.
3. Limper AH. Chemotherapy-induced lung disease. Clin Chest Med 2004; 25: 53-64.
4. Maniwa T, Nakagawa K, Isaka M et al. Pneumothorax associated with treatment for pulmonary malignancy. Interactive Cardiovascular and Thoracic Surgery 2011; 13: 257-261
5. Mori M, Nakagawa M, Fujikawa T et al. Simultaneous bilateral spontaneous pneumothoraces observed during administration of gefitinib for lung adenocarcinoma with multiple lung metastases. Internal Medicine 2005; 44(8): 862-864.
6. Kelly E, Mhurchu EN, Sukor S et al. Chemotherapy-associated recurrent pneumothoraces in lymphangioleiomyomatosis. Respiratory Care 2010; 55(11): 1491-1494.
7. Hsu J-R, Chang S-H, Peng R-P. Pneumothorax following cytotoxic chemotherapy for malignant lymphoma. Chest 1990; 98: 1512-13.
8. Jain TP, Thulka S, Saha S. Extensive pneumothorax, pneumomediastinum and surgical emphysema as a complication of bleomycin therapy. Pediatr Radiol 2005; 35: 1227-1229.
9. Sikkar T, Macvicar D, Husbands JE. Pneumomediastinum complicating bleomycin related lung damage. British Journal of Radiology 1998; 71: 1202-1204.
10. Doll DC. Fatal pneumothorax associated with bleomycin-induced pulmonary fibrosis. Cancer Chemother Pharmacol 1986; 69: 294-5.
11. Quyuumi AA, Ormerod LP, Clarke SW, et al. Pulmonary fibrosis-a serious side effect of amiodarone toxicity. Eur Heart J 1983 Jul;4(7):512-4.
12. Batra MS, Driscoll JJ, Coburn WA. Evansenous nitrous oxide pneumothorax after laparoscopy. Anesth Analg; 1983; 62: 1121-3.
13. Management of trauma. Nitric oxide dangerous in pneumothorax. BMJ 1993; 306(6891):1539.
14. Scannell KA. Pneumothoraces and pneumocystis carinii pneumonia in two AIDS patients receiving aerosolized pentamidine. Chest 1990; 97(2): 479-80.
15. Sepkowitz K, Telzak EE, Blum S et al. Pneumothorax in AIDS. Annals of Internal Medicine 1991; 455-9.
16. Shanley DJ, Luycks BA, Haggerty MF et al. Spontaneous pneumothorax in AIDS patients with recurrent pneumocystis carinii pneumonia despite aerosolized pentamidine. Chest 1991; 99(2): 502-4.
17. Murry CE, Schmidt RA. Tissue invasion by pneumocystis carinii: a possible cause of cavitary pneumonia and pneumothorax. Human Pathology 1992; 23(12): 1380-7.
18. Salas M, Hoffman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiological terminology. American Journal of Epidemiology 1999; 149(11): 981-3.
19. Srinivas S, Varadchary G. Spontaneous pneumothorax in malignancy: a case report and review of the literature. Annals of Oncology 2000; 11: 887-889.
20. Thukral A, Tiwari DN, Sharma N et al. Carcinoma of bronchus presenting as hydropneumothorax. JAPI 2012; 60: 56.
21. Okada D, Koizumi K, Haraguchi S et al. Pneumothorax manifesting primary lung cancer. The Japanese Journal of Thoracic and Cardiovascular Surgery 2002; 50(3): 133-6.
22. Houweling AC, Gijzen LM, Jonker MA et al. Renal cancer and pneumothorax risk in Birt-Hogg-Dube syndrome; an analysis of 115 FLCN mutation carriers from 35 BHD families. Br J Cancer 2011; 105(12): 1912-9.
23. Alonso-Gonzales J, Rodrigues-Pazos L, Fernandez-Redondo V. Birt-Hogg syndrome in a patient with localized fibrocolliculomas and a novel mutation ion the FLCN gene. Intl J Dermatology 2011; 50(8): 867-71.
24. Hauben M, Bate A. Decision support methods for the detection of adverse events in post-marketing data. Drug Discover Today 2009; 14(17-8): 343-57.
25. Greenhouse JB. Commentary: Cornfield, Epidemiology and causality. International Journal of Epidemiology 2009; 38: 1199-1201.
26. Hauben M, Gerrits CM, Reich L et al. Cornfield’s condition applied to data mining output to ascertain confounding. Pharmacoepidemiology and Drug Safety 2005; 14: 582-3.
27. Hauben M, Noren N. A decade of data mining and still counting. Drug Safety 2010; 33(7): 527-34.
28. Brown E. Effects of coding dictionary on signal generation: a consideration of MedDRA compared with WHO-ART. Drug Safety 2002;25(6):445-52.
29. Bate A, et al. A Bayesian neural network method for adverse drug reaction signal generation. European Journal of Clinical Pharmacology 1998; 54(4): 315-21.
30. Hauben M, Reich L. Potential utility of data-mining algorithms for early detection of potentially fatal/disabling adverse drug reactions: A retrospective evaluation. J Clin Pharmacol 2005; 45: 378-84
31. Chen Y, Guo J, Healy DP et al. Risk of hepatotoxicity associated with the use of telithromycin: a signal detection using data mining algorithms. Ann Pharmacotherapy 2008; 42(12): 1791-6.
32. Kubota K, Koide D, Hirai T. Comparison of data mining methodologies using Japanese spontaneous reports. Pharmacoepidemiology and Drug Safety 2004; 13: 387-94.

http://www.medsci.org
33. Hauben M, Aronson J. Defining signal and its subtypes in pharmacovigilance based on a systematic review of previous definitions. Drug Safety 2009; 32(2): 99-110.
34. Engle WA and the Committee on Fetus and Newborn. Surfactant-replacement therapy for respiratory distress in the preterm and term neonate. Pediatrics. 2008; 121(2): 419–432.
35. Van der Ploeg AT. Monitoring of pulmonary function in Pompe disease: a muscle disease with new therapeutic perspectives. Eur Respir J. 2005; 26(6): 984-985
36. Kouroussis C, Mavroudis D, Kakolyris A et al. High incidence of pulmonary toxicity of weekly docetaxel and gemcitabine in patients with non-small cell lung cancer: results of a dose-finding study. Lung Cancer 2004; 44(3): 363-8.
37. Dunsford ML, Mead CM, Bateman AC et al. Severe pulmonary toxicity of gemcitabine-docetaxel combination. Ann Oncol 1999; 10(8): 943-7.
38. Bate A, Edwards IR. Data mining in spontaneous reports. Basic Clin Pharmacol Toxicol 2006; 98(3): 324-30.
39. Abramson I, Wolfson T, Marcotte TD. Extending the p-plot: heuristics for multiple testing. J Int Neuropsychol Soc 1999; 5: 510-517.
40. Raschi E, Piccinni C, Poluzzi E et al. The association of pancreatitis with antidiabetic drug use: gaining insight through the FDA pharmacovigilance database. Acta Diabetol 2011; DOI: 10.1007/s00592-011-0340-7.
41. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiology and Drug Safety 2009; 18(6): 427-36.
42. Motola D, Piccinni C, Biagi C et al. Cardiovascular, ocular and bone adverse reactions associated with thiazolidinediones a disproportionality analysis of the US FDA adverse event database. Drug Safety 2012; 35(4): 315-23.
43. Lapreyre-Mestre M, Grolleau S, Montastruc JL et al. Adverse drug reactions associated with the use of NSAIDs: a case/noncase analysis of spontaneous reports from the French pharmacovigilance database 2002-2006. Fundamental and clinical pharmacology 2013 Apr;27(2):223-30.
44. Tuccori M, Lapi F, Testi A et al. Drug-induced taste and smell alterations: a case/non-case evaluation of an Italian database of spontaneous adverse drug reaction reporting. Drug Safety 2011; 34(10): 849-859.
45. Toccori M, Lapi F, Testi A et al. Statin-associated psychiatric adverse events: a case-non-case evaluation of an Italian database of spontaneous adverse drug reaction reporting. Drug Safety 2008; 31(12): 1115-23.
46. Piccinni C, Marchesini G, Motola D et al. Assessing the association between pioglitazone use and bladder cancer through drug adverse event reporting, Diabetes Care 2011; 34: 1369-1371.
47. Motola D, Vargiu A, Leone R. Hepatic adverse drug reactions: a case/non-case study in Italy. Eur J Clin Pharmacol 2007; 63(1): 73-9.
48. Salvo F, Polimeni G, Cutroneo PM et al. Allergic reactions to oral drugs: A case/non-case study from an Italian spontaneous reporting database (GIF). Pharmacological Research 2008; 58: 2002-2007.