Application of Data Mining and Visualization Techniques for the Prediction of Drug-Induced Nausea in Man

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The therapeutic value of many drugs can be limited by gastrointestinal (GI) adverse effects such as nausea and vomiting. Nausea is a subjective human sensation, hence little is known about preclinical biomarkers that may accurately and effectively predict its presence in man. The aim of this analysis was to use informatics and data-mining tools to identify plausible preclinical GI effects that may be associated with nausea and that could be of potential use in its prediction. A total of 86 marketed drugs were used in this analysis, and the main outcome was a confirmation that nausogenic and non-nausogenic drugs can be clearly separated based on their preclinical GI observations. Specifically, combinations of common preclinical GI effects (vomiting, diarrhea, and salivary hypersecretion) proved to be strong predictors. The model was subsequently validated with a subset of 20 blinded proprietary small molecules and successfully predicted clinical outcome in 90% of cases. This investigation demonstrated the feasibility of data-mining approaches to facilitate discovery of novel, plausible associations that can be used to understand drug-induced adverse effects.

Key Words: nausea; vomiting; predictive value; drug safety; data mining; drug-induced gastrointestinal adverse effects; risk assessment.

Nausea is an unpleasant feeling of sickness, which is accompanied with an urge to vomit although vomiting is not always the result. There are many causes of nausea, including motion, pregnancy, and gastric irritation (Pleuvry, 2009). It can also be a symptom of diseases such as advanced cancer, migraine, or epilepsy as well as an adverse effect of radiotherapy, anesthesia, and drug treatments (Holmes et al., 2009). Nausea and other undesirable gastrointestinal (GI) effects (such as vomiting) can lead some patients to become averse to the drug and avoid further treatment. One example is the development of anticipatory nausea and vomiting (ANV) during cancer chemotherapy, which is seen in approximately 30% of cancer patients (Morrow et al., 1998). ANV is usually described as conditioned response (to the stimuli such as sight of a nurse, smells, and sounds of the treatment room); therefore, it cannot be controlled by antiemetic medication. In addition to reducing patient compliance, drug-induced GI adverse effects can also limit drug absorption and cause dose-limiting toxicity and therefore limit the therapeutic value of many drugs.

Although not life-threatening, drug-induced nausea is a relatively common adverse effect. A recent investigation involving 113 candidate drugs in phase I clinical trials found nausea to be present in approximately 30% of drugs (Ewart et al., 2011). Nausea and vomiting have been associated with late phase development withdrawals. For example, the phase III trial of taspoglutide, a glucagon-like peptide-1 analog, under development for treatment of type 2 diabetes was suspended due to a high incidence of nausea and vomiting (Madsbad et al., 2011). For these reasons, the pharmaceutical industry recognizes the need to assess the risk of drug-induced nausea before promising new drugs are administered to humans rather than leaving the discovery of these effects to costly clinical trials.

Prior to testing any pharmaceutical in man, there is a comprehensive package of in vitro and in vivo tests conducted (Anon., 2009; Ledwith and DeGeorge, 2011). The assessment of nausea, however, in these preclinical studies is extremely controversial. Because it is a subjective human sensation, many argue that there may not be an analogous experience in animals. Nonetheless, it has been reported that some species, such as ferrets, display certain behaviors before emesis (Zaman et al., 2000). However, it remains to be definitely proven that these behaviors truly represent nausea rather than a behavioral prodrome of emesis. Other animal models for assessing nausea include a conditioned taste aversion in rats or mice. Here, animals are exposed to drugs associated with nausea in man and/or vomiting in other species that have emetic reflex. Although they cannot vomit, rodents display gaping reactions after being exposed to these emetic drugs as well as substances previously paired with an emetic drug. This conditioned taste aversion is reported to be a potential model to assess ANV in man (Limebeer et al., 2008; Parker et al., 2002; Seeley et al., 2000).
There are a number of other animal models that, although may not directly predict nausea in man, are used to evaluate other GI side effects of potential drugs. These models include the ferret emesis model successful for example in predicting emetic liability in type 4 phosphodiesterase (PDE4) inhibitors (Macdonald et al., 2000), rodent GI transit e.g., intestinal motility in mice and/or gastric emptying in rats (Reinhart et al., 2005). Although these preclinical studies may indicate that a given drug causes alterations in the GI system, it is likely that there is no single animal model that will accurately and reliably predict drug-induced nausea in man.

The aim of this investigation was (1) to assess whether the risk of drug-induced nausea could be evaluated using a combination of preclinical observations and/or measurements and (2) to quantify the potential association between these preclinical observations and/or measurements with the reports of nausea in man, thus providing potential signals for the prediction of drug-induced nausea in man in advance of clinical testing programs. The analysis was focused on drug-induced nausea that was caused by irritation or distension of the GI tract. In order to achieve this, data were collated using plausible GI observations from preclinical studies from marketed drugs that have been associated with nausea in man. Data from a “negative drug set” (i.e., a set of drugs that were not associated with nausea and their corresponding preclinical GI observations) was included to test the predictive value of the approach. To facilitate the analysis, visualization and clustering tools were used to display the data collected and to discover patterns in preclinical data from past studies and relate them to the presence of nausea, so that this knowledge can be used in future to predict the clinical outcome of new compounds based on their preclinical profile. The benefit of early detection of potential side effects is the confidence that the best drug will get to patients. Therefore, the prediction method presented here could be used to either distinguish among potential candidates during early discovery or to flag a problem of potential nausea, thus enabling either changes to formulation or route of administration or indeed deselection of the candidate. For example, an alternative transdermal formulation of Sumatriptan was recently developed for migraine treatment to avoid nausea and vomiting that previously reduced patients’ compliance (Pierce, 2010).

**MATERIALS AND METHODS**

**GI adverse effect data sources.** Eighty-six marketed drugs on the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) (www.fda.gov/cder/aers) have been used in this analysis. Half of these, labeled the “positive set,” were identified as drugs that are associated with nausea in man. AERS is not a uniform reporting system, therefore some of the adverse events found in the reports may not be relevant. For example, drugs that have been marketed for several years will eventually have some reports of the adverse events associated with their use, including nausea. Therefore, it was necessary to assess the significance of nausea for each of the individual drugs. This was done using the relative reporting (rr) ratio (Clark and Wiseman, 2009). This ratio corresponds to the number of reports of nausea compared with the baseline (i.e., a frequency of nausea over all drugs in the database). The X² test was used to calculate the statistical significance of the rr ratio. Only drugs that had rr ratio higher than 2 and X² value higher than 3.84 were selected for the positive set. The rr ratio was calculated using Equation 1, where “a” is number of AERS reports of nausea for a given drug, “b” is a total number of all other reports in the database, “c” is a total number of all other AERS reports without nausea for a given drug, and “d” is a total number of all other AERS reports without nausea (and not for a given drug):

\[
rr = \frac{a \times (a + b + c + d)}{(a + b) \times (a + c)}
\]

A X² statistic was used to assess the statistical significance using Equation 2, where O is an observed frequency, E is the expected frequency of a certain cell in the contingency matrix, and n is the number of cells (for the 2 × 2 matrix here n = 4).

\[
X^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}
\]

Ninety-seven of all drugs in AERS (> 1500 drugs in total) had rr ratios higher than 2 and X² value higher than 3.84 and 43 of them had at least one plausible GI observation in animals that were available in public domain (i.e., positive set). The other 43 drugs, labeled the negative set,were selected from all the other drugs on AERS, on the basis that they did not have any reports of nausea or had only a small, but statistically not significant number of reports of nausea. All of these 43 negative drugs had at least one plausible GI preclinical observation. A list of all drugs used in this analysis and their therapeutic or pharmacological class is shown in Table 1.

Public domain sources were text mined in order to extract available preclinical GI effects for each of the drugs identified in the positive and negative set. The GI effects included pathology findings (e.g., GI ulcer, gastritis) as well as GI-related clinical observations (e.g., vomiting, salivary hypersecretion, retching). Text mining was done through the AstraZeneca PharmaConnect Knowledgebase, part of the Safety Intelligence Program with Biowisdom (Biowisdom Ltd., www.biowisdom.com). This was supplemented with preclinical data from Elsevier’s PharmaPendium (Pharmapendium, Elsevier B.V., www.pharmapendium.com). The output of text mining was a list of unique preclinical GI observations for all drugs used in this analysis (i.e., unique species-observation pair). Data from all species were then combined, and the final output was a list of unique preclinical observations for each drug. As a result, each observation was only counted once, even if it was reported in two or more species.

**Relative reporting ratio of observations and nausea.** The relative reporting ratio (Equation 1) was used to quantify the link between GI observations and nausea. Here, ‘a’ is the number of times a certain effect is reported for nausea drugs and ‘b’ the number of nausea drugs not showing the effect. ‘c’ is the number of non-nausogenic drugs associated with the effect, and finally ‘d’ is the number of drugs not associated with either the effect or nausea. A X² statistic was used to assess the statistical significance of the rr ratio using Equation 2. To ensure robustness of the statistical methods, an effect needs to have been reported at least five times to be included in the analysis.

**Comparison of preclinical effect distributions.** Kolmogorov-Smirnov (K-S) tests were performed to investigate if there were any differences in the distributions of preclinical effects between nausea and non-nausogenic drugs. The K-S test is a nonparametric test that measures the maximum difference between the two cumulative distributions and was derived to handle continuous distributions. The D value, which corresponds to the maximum vertical difference between two cumulative distributions, was calculated with large values, indicating that the two distributions are different.
Because there are ties in the data, the derived p values should be taken with care, and thus this analysis only focuses on significance and not p values.

The analysis was performed using the statistical package R (v.2.10.1) (R Development Core Team, 2008). A first analysis was made using all identified preclinical effects, and a further analysis was made looking only at GI observations. The number of unique observations was used as the input.

**Derivation of a preclinical profile.** The mined preclinical findings were translated into a binary preclinical profile for each drug. Every bin in the profile corresponded to a specific effect, represented as 1 if the effect was present and as 0 if the effect was absent. Many effects were uncommon, and to facilitate more robust findings, only effects seen for more than three drugs were retained in the profile. Interaction terms between some of the more common effects were calculated—in order to assess them, additional bins were created in a preclinical profile that corresponded to the combinations of the following common observations: vomiting, diarrhea, salivary hypersecretion, and constipation. These combinations were named using abbreviations, for example, V\_3D corresponded to a combination of vomiting and diarrhea SH\_3C to salivary hypersecretion and constipation etc. This resulted in a final profile consisting of 31 variables.

**Two-way clustering of profiles.** To investigate the relationship between the preclinical profile and nausea of drugs, a hierarchical clustering was performed in JMP 7.0 using Ward linking with no pre-treatment of the data. A heat map was created, where the presence of a particular preclinical finding
was colored red. All drugs (both from positive and negative set) were clustered based on the preclinical observations profile. Clustering is a mathematical method that quantifies the similarity between the drugs used in this investigation allowing grouping of drugs that are similar. Thus, the preclinical profiles of drugs in different clusters are considered different. In the heat map, drugs associated with nausea were colored blue, and drugs not associated with nausea were colored red.

**Validation of the model.** The derived preclinical profile was validated using 20 blinded AstraZeneca proprietary small molecules from various therapy areas, which had all completed a phase I clinical trial. Preclinical findings were extracted from legacy reports and mapped to the terms used in the previous analysis. A new clustering was performed on the 106 compounds (i.e., 86 marketed drugs and 20 proprietary compounds), and clinical outcome was predicted for the blinded 20 compounds, based on their cluster neighbors. The class prediction (i.e., nausogenic or non-nausogenic) was then compared with the actual class of each compound. The actual class was assigned using data from phase I studies. Compounds have been identified as nausogenic if nausea has been observed in either (a) more than 30% volunteers in two or more dose groups or (b) more than 30% of volunteers in the highest dose group. In addition, if nausea was observed in the placebo group, the percentage of volunteers that had nausea in the placebo group was lower than in the dose group. If compounds did not meet these criteria, they were classified as non-nausogenic.

**Data visualization.** Cytoscape (Shannon et al., 2003) was used to create a visual display of the vast network of associations between the observations in the preclinical studies and drug-induced nausea. Cytoscape is an open-source network visualization, and analysis software that enables researchers to create networks using underlying associations within their datasets (here, the relationship between preclinical GI effects and nausea). Network visualization is an interactive process that can be used to extract useful information or identify patterns and/or connections that may not be obvious in the original dataset. To separate the noise from the more significant findings, additional clustering was performed on the 106 compounds (i.e., 86 marketed drugs and 20 proprietary compounds), and clinical outcome was predicted for the blinded 20 compounds, based on their cluster neighbors. The class prediction (i.e., nausogenic or non-nausogenic) was then compared with the actual class of each compound. The actual class was assigned using data from phase I studies. Compounds have been identified as nausogenic if nausea has been observed in either (a) more than 30% volunteers in two or more dose groups or (b) more than 30% of volunteers in the highest dose group. In addition, if nausea was observed in the placebo group, the percentage of volunteers that had nausea in the placebo group was lower than in the dose group. If compounds did not meet these criteria, they were classified as non-nausogenic.

**Results**

The objective of this analysis was to assess whether preclinical GI observations and/or measurements can be used to evaluate the risk of drug-induced nausea in man. This was achieved by collating and comparing two sets of data—one containing preclinical GI observations reported for drugs that are associated with nausea (positive set) and one for drugs that are not nausogenic (negative set). Clear differences between the two sets of drugs were found.

**Comparison of Distributions**

First, the difference between the distribution of preclinical effects for the nauseous and non-nauseous drugs was inspected (Fig. 1a). There was a statistically significant ($\alpha = 0.05$) difference between the nauseous and non-nauseous drugs ($D = 0.3256$) indicating that nauseous drugs in general tend to have more preclinical observations associated with them. The differences were even more pronounced, with a $D$ value of 0.6279, if only GI effects were analyzed (Fig. 1b).

**Frequency of Preclinical Observations**

A list of preclinical GI observations that were most common in the positive and negative set of drugs can be found in Table 2. The most common observations reported for the drugs associated with nausea were vomiting (81.4%), diarrhea (72.1%), and salivary hypersecretion (67.4%). These effects were observed in the negative set of drugs; however, they were much less common; vomiting was reported only in 39.5% of negative drugs, diarrhea in 34.9%, and salivary hypersecretion in only 18.6%. In addition to vomiting, diarrhea, and salivary hypersecretion, other commonly reported GI observations included GI ulcers, salivary gland disorders, and constipation. Interestingly, each of these was observed more often in the positive set of drugs compared with the negative set of drugs.

A total of 78 different preclinical GI effects were found that were reported for drugs used in this analysis. These effects were reported in 11 different species; rat, mouse, hamster, dog, cat, rabbit, horse, pig, monkey, guinea pig, and ferret. The most common effect reported in the positive set of drugs (Table 3) was vomiting in dogs (observed for 72.1% of all drugs associated with nausea), whereas vomiting in dogs was only

![FIG. 1.](http://toxsci.oxfordjournals.org/)

(a) Number of “all” unique preclinical effects found for each drug, sorted ascendantly for each set of drugs. (b) Number of unique “GI” preclinical effects found for each drug, sorted ascendantly for each set of drugs. The x-axis represents total number of drugs in each set ($n = 43$). Solid and dashed lines correspond to positive and negative set respectively.
TABLE 2
Most Common Preclinical GI Effects Observed in Positive (i.e., Drugs That are Associated With Nausea, Left) and Negative Set (Drugs That Are Not Associated With Nausea, Right). The Percentage of All Drugs for Which a Given Effect Was Observed Is Indicated for Both Sets

<table>
<thead>
<tr>
<th>Effect</th>
<th>Positive set %</th>
<th>Negative set %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>81.4</td>
<td>39.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>72.1</td>
<td>34.9</td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td>67.4</td>
<td>18.6</td>
</tr>
<tr>
<td>GI ulcer</td>
<td>37.2</td>
<td>11.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>37.2</td>
<td>9.3</td>
</tr>
<tr>
<td>GI disorder</td>
<td>32.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Gastritis</td>
<td>27.9</td>
<td>9.3</td>
</tr>
<tr>
<td>Pancreatic disorder</td>
<td>27.9</td>
<td>7.0</td>
</tr>
<tr>
<td>Salivary gland disorder</td>
<td>14.0</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3
Most Common Preclinical GI Effects Observed in a Given Species. The Percentage of All Drugs for Which a Given Effect in a Given Species Was Observed Is Indicated for Both Sets

<table>
<thead>
<tr>
<th>Effect</th>
<th>Species</th>
<th>Positive set %</th>
<th>Negative set %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Dog</td>
<td>72.1</td>
<td>30.2</td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td>Dog</td>
<td>46.5</td>
<td>16.3</td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td>Rat</td>
<td>44.2</td>
<td>14.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Dog</td>
<td>44.2</td>
<td>11.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Monkey</td>
<td>27.9</td>
<td>9.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Monkey</td>
<td>27.9</td>
<td>9.3</td>
</tr>
<tr>
<td>GI ulcer</td>
<td>Rat</td>
<td>25.6</td>
<td>9.3</td>
</tr>
<tr>
<td>GI ulcer</td>
<td>Rat</td>
<td>20.9</td>
<td>7.0</td>
</tr>
<tr>
<td>GI disorder</td>
<td>Rat</td>
<td>16.3</td>
<td>7.0</td>
</tr>
<tr>
<td>GI ulcer</td>
<td>Dog</td>
<td>16.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Cat</td>
<td></td>
<td>7.0</td>
</tr>
</tbody>
</table>

reported in 30% of all negative compounds; therefore, it was 2.5 times less common than in the positive set (72% in the positive set). Salivary hypersecretion in dog was the next most commonly observed effect with 46.5% of drugs in the positive set reporting this finding. Salivary hypersecretion in dogs was four times less likely to be reported in the negative set than in drugs associated with nausea (11.6% in the negative set, compared with 46.5% in the positive set). The rat (44.2%) demonstrated a high incidence of salivary hypersecretion.

Other observations, that were reported much more often in the positive set, as compared with the negative one, were GI ulcer in dogs (seven times more likely to be observed in drugs associated with nausea; i.e., 16.3% in positive set, compared with only 2.3% in the negative one), diarrhea in dog (greater than six times more likely to be observed in drugs associated with nausea; i.e., 44.2% in the positive set, compared with only 7% in the negative one), and diarrhea in monkey (six times more likely observed in the positive set).

Using the cytoscape software, it was possible to visualize how the preclinical GI effects reported for the drugs in this analysis were associated with nausea and the frequency of the effect (Fig. 2). Many of the preclinical effects were linked to both the 'nausea' and 'no nausea' nodes, indicating that they were observed in both sets of drugs. Furthermore, the lines connected to the nausea node are thicker, indicating that there was a higher frequency of these effects in the nausogenic drugs.

**Linking Effects to Nausea**

To quantify the link between GI observations and nausea, the relative reporting ratio was calculated together with a $X^2$ statistic. Only effects that were seen more than five times were included in analysis. A total of 16 effects fit this criteria and 8 of these had statistically significant ($X^2 > 3.84$) relative reporting ratios greater than 1.5 (Table 4).

Nausea is a complex reflex so it was investigated whether combinations of two or more common effects were better predictors of nausea than reporting of one effect alone. Fig. 3 shows the pairwise combinations of the more common effects and their frequency in positive and negative drug sets. By expanding the combinations to a full GI effect, the profile provides the possibility to compare nauseous with non-nauseous drugs taking all of these effects into account.

**Two-Way Clustering**

The derived GI profiles of marketed drugs were clustered using JMP7.0. The derived clusters show a clear grouping of nauseous and non-nauseous drugs, with nauseous drugs at the bottom of the graph with many effects and non-nausea drugs primarily found at the top (Fig. 4).

When 20 blinded compounds were added and new clustering was performed, it was possible to make a clinical outcome prediction for new compounds, based on their cluster neighbors. Out of the 20 blinded proprietary compounds used in the validation, 18 compounds were predicted correctly (90% true positive prediction and 90% true negative prediction). Details of validation set are provided in the Supplementary Material.

**DISCUSSION**

The aim of this analysis was to evaluate whether GI observations from preclinical studies can be used to assess the risk of drug-induced nausea in man. In the analysis presented here, we have focused only on GI preclinical observations and have substantiated the analysis by quantifying the associations.
There were clear differences between nauseous and non-nauseous drugs based on their distribution of preclinical effects (Fig. 1). Nauseous drugs in general tended to have more preclinical observations associated with them. The differences were even more pronounced when only GI effects were analyzed. This result suggests that nauseous drugs have more GI preclinical observations than non-nauseous drugs, but this difference was not only due to the fact that they have more preclinical observations in general. If that was the case, graphs “a” and “b” in Figure 1 would have very similar profiles, while it can be seen that the separation between positive and

<table>
<thead>
<tr>
<th>Effect</th>
<th>Positive set</th>
<th>Negative set</th>
<th>$r$</th>
<th>$X^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal disorder</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>5.31</td>
</tr>
<tr>
<td>GI disorder</td>
<td>14</td>
<td>2</td>
<td>1.75</td>
<td>11.1</td>
</tr>
<tr>
<td>Pancreatic disorder</td>
<td>12</td>
<td>2</td>
<td>1.71</td>
<td>8.53</td>
</tr>
<tr>
<td>Gastritis</td>
<td>12</td>
<td>2</td>
<td>1.71</td>
<td>8.53</td>
</tr>
<tr>
<td>Salivary gland disorder</td>
<td>6</td>
<td>1</td>
<td>1.71</td>
<td>3.89</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>3</td>
<td>1.68</td>
<td>11.4</td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td>29</td>
<td>8</td>
<td>1.56</td>
<td>20.9</td>
</tr>
<tr>
<td>GI ulcer</td>
<td>16</td>
<td>5</td>
<td>1.52</td>
<td>7.62</td>
</tr>
</tbody>
</table>

**TABLE 4**

**Effects With Statistically Significant Relative Reporting Ratios Greater Than 1.5**

**FIG. 3.** Graph showing the number of drugs exhibiting at least two of the following effects, vomiting (V), diarrhea (D), salivary hypersecretion (SH), and constipation (C).
FIG. 4. Two-way clustering of preclinical effects and drugs. Drugs causing nausea colored blue and non-nausea drug colored red. In the heatmap, the presence of a particular preclinical finding is colored red. Four clusters can be distinguished (from the top): cluster 1 (33 of 40 are non-nausea drugs), cluster 2 (7 of 10 drugs are nauseous), cluster 3 (10 of 15 drugs are nauseous), and cluster 4 (19 of 21 drugs are nauseous).
negative sets are more pronounced in b. This indicates that there are differences in the GI profiles between nauseous and non-nauseous drugs.

The analysis revealed that vomiting (81.4%), diarrhea (72.1%), and salivary hypersecretion (67.4%) were the most common preclinical GI observations in drugs associated with nausea (Table 2). It was not surprising to see that these types of GI effects were most common in the drugs associated with nausea because vomiting often (but not always) follows nausea. Furthermore, 11 of the 43 drugs in the positive set were within the anticancer therapeutic class, whereas only 1 of the 43 drugs in the negative set belonged to this therapeutic class (Table 1). Anticancer therapies are well documented to be nausea-inducing, and the 43 drugs in the negative set belonged to this therapeutic class (Table 1).

Salivation, intense licking, chewing, and swallowing have been associated with vomiting in many species, including dog, monkey, and pig (Grélot et al., 1998; Lang et al., 1993; Mattsson and Yochmowitz, 1980), and therefore, they have been suggested to be prodromal behaviors of impending vomiting. Although these preclinical effects have been expected to have association with nausea, here we were able to quantify these associations. Indeed, the most common preclinical GI effect observed for positive drugs were not unique but were reported in the negative set of drugs. However, the frequency of these observations was greater in nauseous than in non-nauseous drugs. In addition to this, some species were more predictive than others for given effects. For example, diarrhea in dog or monkey was six times more likely to be observed in the drugs associated with nausea (Table 3), whereas in the rat, it was only slightly more frequent (21 and 16% in the positive and negative set, respectively). This information is important because the onset of this preclinical effect in dogs or monkeys should be given careful consideration about potential adverse effects in man, and these two are often species used in toxicology testing prior to first time in man administration.

Interestingly, vomiting and diarrhea both had a rather low rr of 1.34, suggesting that although they were the most common preclinical observations in the positive set, on their own neither of them were predictive of nausea in man. It is widely recognized that dogs vomit in conjunction with dosing, e.g., for bitter tasting compounds, and hence single observation is not a strong linker to nausea in man. However, the data clustering indicated that if both of these effects were seen together or one of them was seen in combination with another GI effect, then this greatly increased the likelihood of nausea in man. This finding confirmed our earlier suggestion that since nausea is a complex reflex, the combinations of GI effects were better predictors than individual effects alone. Indeed, the main driving force for clustering shown in Figure 4 was the presence of more than one of the following observations: constipation, diarrhea, salivary hypersecretion, or vomiting. There appears to be four larger clusters (naming from the top of Fig. 4): Cluster 1, containing compounds exhibiting few observations, of which most are non-nauseous. Both clusters 2 (10 drugs) and 3 (15 drugs) are comprised of both nausea and non-nausea compounds, but with a majority of them showing nausea. The main driver for these drugs to cluster appears to be the presence of both salivary hypersecretion and vomiting or diarrhea and vomiting. It appears as if there are additional observations, this often indicates that the drug is nauseous. The final cluster 4 contains drugs that show vomiting, salivary hypersecretion, and diarrhea providing a strong link to nausea.

Although much of the clustering was anticipated, the drugs breaking the pattern are potentially more interesting for further investigations.

Glucagon was the only drug associated with nausea that had diarrhea as its only GI effect. However, glucagon has the second fewest publicly known preclinical observations of all the drugs in this study, and the question arises as to whether this drug truly does not cause many adverse effects or if this is due to limitations of publically available data. Glucagon is strongly associated with nausea in man as documented in AERS, the FDA approval package document and peer-reviewed publications (Mohiki et al., 1998; Ranganath et al., 1999; Van Dam et al., 1995). Therefore, it was correctly identified as nauseous drug and was included in the positive set. The mechanism of glucagon-induced nausea is unclear; it has been suggested that the adverse effect may be a result of direct effect on the brain or alternatively, a result of the inhibition of proximal small intestine (Ranganath et al., 1999).

If glucagon indeed is causing nausea through direct effect on the brain, it may be possible that it does not cause an irritation in the GI tract; therefore, it may not have many preclinical GI observations. However, there was not enough evidence to support this, and the lack of preclinical effects may be simply due to the limited availability of the data in public domain. This example highlights the limitation of using data from public sources, and we envisage that having more complete information about a drug (i.e., knowledge of negative findings) would improve confidence in establishing a link between preclinical profile and nausea.

Another example of a nauseogenic drug found in a mainly non-nausogenic cluster was flavoxate, an anticholinergic to relieve pain when urinating. As with glucagon, it was associated with very few preclinical observations. Further investigation confirmed that flavoxate had occasional reports of nausea; however, it was noted that symptoms were usually mild (FDA approval package document). Taking into account that flavoxate is used to relieve symptoms of infections of the prostate, bladder, or kidneys, conditions frequently associated with nausea and abdominal pain, it is possible that the nauseous effect might be a result of the condition and not the actual drug.

There are important lessons to be learned from inspecting the non-nausea causing drugs found in clusters mainly populated by nauseous drugs. For instance, epinastine and felbamate both gave rise to vomiting, diarrhea, and salivary hypersecretion. Further investigations, however, show that epinastine is used...
clinically as eye drops, whereas in most preclinical studies either iv or oral administration was used. It is therefore not unlikely that this drug might potentially cause nausea if were it administered systemically. Furthermore, this shows how local administration of drugs might mitigate risk of nausea in man. The case of felbamate highlights a potential pitfall when working with AERS data. Only 7 of a total of 172 AERS felbamate reports have indications of nausea, which does not support a statistically significant link between the drug and nausea. However, an FDA approval package document states that nausea has been often reported in clinical trials (PharmaPendium and Palmer and McTavish, 1993). Therefore, felbamate should probably have been considered nausogenic. Furthermore, this indicates that an analysis such as the one performed here might benefit from employing data from multiple sources.

It is important to note that the analysis presented here does not take into account drug exposures that produced preclinical observations and how these related to the exposures reached in man at therapeutic doses. This is one of the limitations of text-mining and using data from public sources, i.e., exposures are often not available or only limited information is provided (e.g., dose level but not pharmacokinetic data and plasma levels of a drug). However, despite this limitation, our results imply that the detailed qualitative analysis of the preclinical profile can indicate whether the drug has the potential to cause nausea in man.

The results from the validation using 20 blinded proprietary compounds showed that our model successfully predicted the outcome in man (in phase I trials) in 90% of cases. This implies that the clusters derived using retrospective data from marketed drugs are relevant for predicting nausea for in development compounds. Inspection of the mispredicted compounds identified some challenges with combining data from different sources i.e., that have different terminology. This highlights the need for a well-curated and accepted ontology.

This investigation demonstrates the feasibility of data-mining approaches to facilitate discovery of novel, plausible associations that can be used to understand drug-induced adverse events. Utilizing existing public and/or proprietary data sets negates the need for additional animal usage and in cases such as the prediction of nausea, where there is no validated animal model, can result in accurate prediction of such an effect prior to compound testing in man. The results of the work presented here indicate that the data that is already collected as a part of mandatory preclinical studies can be additionally used to assess a risk of drug-induced nausea in man. Therefore, without an increase in demand on animals, the data that is already collected can aid decision-making. For example, if a selection of new chemical entities is tested in preclinical studies and only one compound can be taken forward into First Time In Man study, the integrated analysis presented here can be used to differentiate between otherwise similar compounds.

CONCLUSIONS

This investigation has shown that there are clear differences in the preclinical profile between nausogenic and non-nausogenic drugs. The results presented here show that there was a set of unique preclinical observations that were good markers of nausea on their own (salivary hypersecretion and constipation). In addition, combination of common preclinical effects (e.g., vomiting, diarrhea, salivary hypersecretion) increased likelihood of drug-induced nausea in man. Using two-way clustering, it was possible to separate nausogenic and non-nausogenic drugs based on their preclinical GI observations aiding the risk assessment of drug-induced nausea before a new compound reaches human. Finally, this approach was tested using blinded proprietary compounds and the model successfully predicted the results in man in 90% of cases. Consequently, we showed that our model can be used to predict clinical outcome based on the preclinical profile of a compound, prior to testing in man. We propose that such prediction can be made routinely for all development compounds, without any additional animal testing.

This work also highlights the usefulness of visual tools for displaying a large amount of data. For example, using a visual network to plot many preclinical effects that are associated with drug-induced nausea in man can help to quickly identify the most relevant findings. Increasingly, research scientists are relying on informatics and data-mining approaches to help organize the vast data sets and literature on their topic of study as well as helping them to discover novel and plausible associations and yield new hypothesis.

SUPPLEMENTARY DATA

Supplementary data are available online at http://toxsci.oxfordjournals.org/.

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