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Contributors: KH initiated the study and contributed to the design, interpretation, and reporting. ET coordinated the collection of the data and contributed to the study design, interpretation, and reporting. JD conducted the statistical analyses and contributed to the interpretation and reporting. LA and DG contributed to the design of the study, data collection, interpretation, and reporting. JC and OB contributed to database design, data collection, and reporting. KH is guarantor for the study.

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Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study

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Abstract

Objectives To examine the relation between antipsychotic drugs and myocarditis and cardiomyopathy.

Design Data mining using bayesian statistics implemented in a neural network architecture.

Setting International database on adverse drug reactions run by the World Health Organization programme for international drug monitoring.

Main outcome measures Reports mentioning antipsychotic drugs, cardiomyopathy, or myocarditis.

Results A strong signal existed for an association between clozapine and cardiomyopathy and myocarditis. An association was also seen with other antipsychotics as a group. This association was based on sufficient cases with adequate documentation and apparent lack of confounding to constitute a signal. Associations between myocarditis or cardiomyopathy and lithium, chlorpromazine, fluphenazine, haloperidol, and risperidone need further investigation.

Conclusions Some antipsychotic drugs seem to be linked to cardiomyopathy and myocarditis. The study shows the potential of Bayesian neural networks in analysing data on drug safety.

Introduction

The antipsychotic drug clozapine has been reported to cause myocarditis or cardiomyopathy.1 2 Other drugs in the same therapeutic class may share similar toxicity. Data mining of a large database of suspected adverse reactions can find such new signals. As part of the World Health Organization’s programme for international drug monitoring, national pharmacovigilance centres in 60 countries report adverse reactions to a central database maintained by the Uppsala Monitoring Centre in Sweden.3

To analyse this large database an approach using Bayesian statistics implemented in a neural network architecture has been developed. The approach is able to look for new adverse reactions from combinations of drugs and also to identify previously unknown patterns, such as risk factors for adverse events with specific drugs—for example, patient age, underlying diseases, and drug interactions. We used the Bayesian approach to look for cardiac effects related to antipsychotic drugs in the WHO database of adverse reactions.

Methods

We used the Bayesian confidence propagation network, which implements Bayesian statistics in a neural network architecture, in the WHO database. The network was used to test reports of clozapine and all other antipsychotic drugs suspected of causing myocarditis or cardiomyopathy against a background of all reports in the database. We calculated the strength of dependency between a drug (or drug group) and adverse reaction using a logarithmic measure of disproportionality called the information component.4 An association between the drug and the reaction was considered significant if the information component minus 2 standard deviations was positive. The value of the information compo-
null

Results

Myocarditis and cardiomyopathy were reported rarely as suspected adverse drug reactions, accounting for less than 0.1% (2121) of almost 2.5 million reports. The table shows the antipsychotic drugs reported to have caused either myocarditis or cardiomyopathy on two or more occasions. Clozapine has a much higher information component than other antipsychotics together and than the general background database. Most reports predated recent publicity about clozapine. The statistical associations of clozapine with myocarditis and cardiomyopathy individually were also significant. The group of other antipsychotics drugs was significantly associated with myocarditis and cardiomyopathy together (table) and individually compared with the general database, although these associations were much weaker than for clozapine.

Chlorpromazine, lithium, and fluphenazine were significantly associated with myocarditis and cardiomyopathy. The 16 cases with risperidone were not more than expected given the high overall reporting of the drug in the database. Chlorpromazine was also significantly associated with myocarditis and cardiomyopathy separately. Lithium, fluphenazine, and risperidone were significantly associated with cardiomyopathy but not myocarditis. In contrast, haloperidol was associated with myocarditis but not cardiomyopathy.

Discussion

Our analysis suggests that antipsychotic drugs other than clozapine may be associated with myocarditis and cardiomyopathy. The findings may have three explanations. The conditions for which antipsychotics are used could be risk factors for myocarditis and cardiomyopathy; the antipsychotic drug could be an innocent bystander; or there may be a causal association. Despite patients taking clozapine being intensively monitored for agranulocytosis, the former two are unlikely explanations for the strong relation between clozapine and myocarditis and cardiomyopathy. The association with clozapine cannot be explained by coprescribed drugs. In some of the cases in the other antipsychotics group the patient was also taking clozapine or non-antipsychotic drugs known to cause myocarditis or cardiomyopathy. However, standardised clinical evaluation shows that there were sufficient cases with adequate documentation and apparent lack of confounding to constitute a signal for cardiomyopathy or myocarditis in the other antipsychotics identified above.

Choice of methods

Our results were obtained by a data mining approach. A concern had been raised about myocarditis with clozapine. We then examined the association between the group of antipsychotics with myocarditis and cardiomyopathy. Having discovered a quantitative association between the antipsychotics group and cardiomyopathy and myocarditis, we investigated individual antipsychotic drugs and then performed a case by case analysis. Our study shows that data mining can be used successfully to detect signals of adverse reactions in the WHO database.

Our results could have been shown using a simpler method. However, the simpler methods rely on someone deciding to look for an association. A data mining approach that routinely looks for associations between all possible combinations of drugs and adverse reactions is computer intensive (hence the use of a neural network). However, it increases the objectivity of signal detection by introducing an effective quantitative filtering step before clinical analysis. We believe that this is enormously beneficial.

Implications

The summaries of case histories in the database do not allow us to draw definite conclusions about the likelihood of the possible causes of the associations we observed between antipsychotic drugs and myocarditis and cardiomyopathy. Adverse drug reactions are

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**Antipsychotic drugs (anatomical, therapeutic, chemical drug classification N05A) for which two or more reports of cardiomyopathy or myocarditis have been registered in WHO database**

<table>
<thead>
<tr>
<th>Drug</th>
<th>No of case reports</th>
<th>Total No of reports for drug</th>
<th>Information component</th>
<th>Information component − 2SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>231</td>
<td>24 730</td>
<td>3.34</td>
<td>3.14</td>
</tr>
<tr>
<td>Other antipsychics*</td>
<td>89</td>
<td>60 775</td>
<td>0.71</td>
<td>0.40</td>
</tr>
<tr>
<td>Lithium</td>
<td>17</td>
<td>6 315</td>
<td>1.45</td>
<td>0.76</td>
</tr>
<tr>
<td>Risperidone</td>
<td>16</td>
<td>10 146</td>
<td>0.69</td>
<td>−0.01</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>14</td>
<td>5 386</td>
<td>1.38</td>
<td>0.63</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>11</td>
<td>8 557</td>
<td>0.53</td>
<td>−0.31</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>8</td>
<td>2 242</td>
<td>1.59</td>
<td>0.62</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>8</td>
<td>6 135</td>
<td>0.48</td>
<td>−0.48</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>5</td>
<td>3 973</td>
<td>0.41</td>
<td>−0.77</td>
</tr>
<tr>
<td>Perhexazine</td>
<td>2</td>
<td>317</td>
<td>1.23</td>
<td>−0.45</td>
</tr>
<tr>
<td>Pimozide</td>
<td>2</td>
<td>536</td>
<td>1.02</td>
<td>−0.65</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>2</td>
<td>709</td>
<td>0.88</td>
<td>−0.79</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>2</td>
<td>1 703</td>
<td>0.26</td>
<td>−1.41</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>2</td>
<td>623</td>
<td>0.85</td>
<td>−0.72</td>
</tr>
</tbody>
</table>

*All antipsychotic drugs other than clozapine.

In this table a single case report is counted for more than one drug adverse reaction combination if there are two or more suspected antipsychotic drugs in that case report.
Effect of improved housing on illness in children under 5 years old in northern Malawi: cross sectional study
Christopher G Wolff, Dirk G Schroeder, Mark W Young

Abstract

Objective To evaluate the effects of a Habitat for Humanity housing improvement programme in northern Malawi on the prevalence of childhood illnesses.

Design Household based cross sectional study.

Setting Rural communities centred near the small northern Malawi town of Ekwendeni.

Subjects 318 children under 5 years old.

Main outcome measures Prevalence of respiratory, gastrointestinal, and malarial infections according to maternal recall, laboratory, or clinical data.

Results Children living in improved homes were less likely to have respiratory, gastrointestinal, or malarial illnesses (odds ratio 0.56, 95% confidence interval 0.35 to 0.91) after confounding factors were controlled for. The reductions in individual diseases were not significant.

Conclusion Improved housing significantly reduced the burden of disease among children under 5 years old.

Introduction

Poor quality housing is generally accepted to be an important contributor to ill health. Rates of disease have been associated with the quality and specific attributes of a house as well as the conditions that those attributes impose. Antipsychotic drugs should also be considered in unexplained sudden deaths in psychotic patients.

We thank the national centres that contribute data to the WHO international drug monitoring programme. The opinions and conclusions, however, are not necessarily those of the various national centres or of the WHO. Roland Orre was central in developing the bayesian confidence propagation neural network as a routine tool for signal detection in the WHO database of drug adverse reactions.

Contributors: DMC suggested the study and made a provisional investigation of the data, AB and IRE planned and designed the study; AB carried out the study; and IRE, AB, and ML evaluated the results. RHBM drafted the first report of the study, AB and IRE wrote the paper, and all authors contributed to modifying the manuscript and the final editing of the paper.

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