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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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1 Hawton K, Fagg J, Simkin S, Bale E, Bond A. Trends in deliberate self-harm in Oxford, 1985-1995. Implications for clinical services and the prevention of suicide. *Br J Psychiatry* 1997;171:556-60.
2 Bialas MC, Reid PG, Beck P, Lazarus JH, Smith P M, Scorer RC. Changing patterns of self-poisoning in a UK health district. *Q J Med* 1996;89:893-901.
3 Spooner JB, Harvey JG. Paracetamol overdoses—facts not misconceptions. *Pharm J* 1993; May 22:706-7.
4 Bray GP. Liver failure induced by paracetamol. *BMJ* 1993;306:157-8.
5 Gunnell D, Hawton K, Murray V, Garnier R, Bismuth C, Fagg J, et al. Use of paracetamol for suicide and non-fatal poisoning in the UK and France: are restrictions on availability justified? *J Epidemiol Community Health* 1997;51:175-9.
6 O'Grady J. Acute liver failure. *Medicine* 1999;27:80-2.
7 Committee on Safety of Medicines, Medicines Control Agency. Paracetamol and aspirin. *Curr Probl Pharmacovigilance* 1997;23:9.
8 Hawton K, Ware C, Mistry H, Hewitt J, Kingsbury S, Roberts D, et al. Paracetamol self-poisoning. Characteristics, prevention and harm reduction. *Br J Psychiatry* 1996;168:43-8.
9 Hawton K, Ware C, Mistry H, Hewitt J, Kingsbury S, Roberts D, et al. Why patients choose paracetamol for self poisoning and their knowledge of its dangers. *BMJ* 1995;310:164.
10 Charlton J, Kelly S, Dunnell K, Evans B, Jenkins R, Wallis R. Trends in suicide deaths in England and Wales. *Popul Trends* 1992;69:10-6.
11 Prince MI, Thomas SHL, James OFW, Hudson M. Reduction in incidence of severe paracetamol poisoning. *Lancet* 2000;355:2047-8.
12 Poulin C. Prevention of paracetamol poisoning. *Lancet* 2000;355:2010-1.
13 Atcha Z, Majeed A. Paracetamol related deaths in England and Wales, 1993-97. *Health Statistics Q* 2000;7:5-9.
14 Harrison PM, O'Grady J, Keays RT, Alexander GJ, Williams R. Serial prothrombin time as a prognostic indicator in paracetamol induced fulminant hepatic failure. *BMJ* 1990;301:964-6.
15 Turvill JL, Burroughs AK, Moore KP. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. *Lancet* 2000;355:2048-9.

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

David M Coulter, Andrew Bate, Ronald H B Meyboom, Marie Lindquist, I Ralph Edwards

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. The 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-

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nent is based on the number of case reports for drug(s) "x" (Cx); the number of case reports of adverse reaction(s) "y" (Cy); the number of reports of the specific combination (Cxy); and the total number of reports (C). Further details of the methods are available on the *BMJ*'s website.

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.[5] 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[6] 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.

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

Drug	No of case reports	Total No of reports for drug	Information component	Information component –2SD
Clozapine	231	24 730	3.34	3.14
Other antipsychotics*	89	60 775	0.71	0.40
Lithium	17	6 315	1.45	0.76
Risperidone	16	10 746	0.69	–0.01
Chlorpromazine	14	5 386	1.38	0.63
Haloperidol	11	8 257	0.53	–0.31
Fluphenazine	8	2 242	1.59	0.62
Olanzapine	8	6 135	0.48	–0.48
Thioridazine	5	3 973	0.41	–0.77
Pericyazine	2	317	1.23	–0.45
Pimozide	2	536	1.02	–0.65
Quetiapine	2	709	0.88	–0.79
Trifluoperazine	2	1 703	0.26	–1.41
Zuclopenthixol	2	623	0.95	–0.72

*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.

What is known on this topic

Clozapine has been reported to be associated with myocarditis and cardiomyopathy

What this study adds

The WHO database shows that clozapine is significantly more frequently reported in relation to cardiomyopathy and myocarditis than other drugs

Myocarditis and cardiomyopathy were also particularly associated with chlorpromazine, lithium, fluphenazine, risperidone, and haloperidol

These associations need to be investigated further to establish whether they are causal

Data mining is a useful tool in pharmacovigilance

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 or 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.[7] 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.[8] 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

greatly underreported worldwide. Further study is needed to determine if antipsychotics other than clozapine cause myocarditis or cardiomyopathy, particularly lithium, chlorpromazine, fluphenazine, haloperidol, and risperidone, and to consider the comparative risks and effectiveness of antipsychotics. This is especially important given the recent finding that older and newer drugs have similar efficacy.[9] 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. IRE is the guarantor.

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1 Jensen VE, Gotzsche O. Allergic myocarditis in clozapine treatment. *Ugeskrift for Laeger* 1994;156:4151-2.
2 Killian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999;354:1841-5.
3 Olsson S. The role of the WHO programme on international drug monitoring in coordinating worldwide drug safety efforts. *Drug Safety* 1998;19:1-10.
4 Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol* 1998;54:315-21.
5 Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the clozaril national registry. *J Clin Psychiatry* 1998;59(suppl 3):3-7.
6 Edwards IR, Lindquist M, Wiholm B-E, Napke E. Quality criteria for early signals of possible adverse drug reactions. *Lancet* 1990;336:156-8.
7 Hand DJ. Statistics and data mining: intersecting disciplines. *SIGKDD Explorations* 1999;1:16-9.
8 Edwards IR. Adverse drug reactions: finding the needle in the haystack. *BMJ* 1997;315:500.
9 Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ* 2000;321:1371-6.

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Effect of improved housing on illness in children under 5 years old in northern Malawi: cross sectional study

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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.[1] Rates of disease have been associated with the quality and specific attributes of a house as well as the conditions that those qualities impose.[2–11]

Although the importance of housing for health is recognised,[1 12 13] few well designed studies have quantified this impact, especially in the developing world. The objective of this study was to assess the impact on children's health of a housing improvement project in rural Malawi. We examined the effect on illness of living in improved housing compared with living in traditional housing.

Participants and methods

The study was conducted in collaboration with Ekwendeni Hospital, Homeless International UK, and Habitat for Humanity International in the town of Ekwendeni, Malawi. Traditional houses in the area are constructed of mud brick walls with thatch roofing, hard packed mud floors, and possibly a pit latrine. Houses are usually about 25 m^2 and consist of two or three rooms. Houses constructed under the Habitat for Humanity programme in Ekwendeni have fired mud bricks, tile roofing, concrete foundation, and a pit latrine. Habitat houses have a mean size of 30 m^2 and three rooms. The cost of a habitat house at the time of the study was about $550 (£370), offset by a 10 year no interest loan. Habitat houses were built next to or replaced the traditional house of the intended owner and were non-systematically dispersed throughout the communities among traditional houses.

Participants in the habitat programme were selected by a village habitat committee. Applicants had to be unable to provide adequate housing for themselves because of financial, social, or physical reasons and to have shown their commitment to the programme by spending a standardised amount of time helping to build another applicant's house.

Sample

We used data from two surveys conducted in March and August 1997. Households for the first survey were randomly selected from a list of about 300 habitat

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