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Haematological safety of antipsychotic drugs

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Many clinicians have become concerned about the safety of new antipsychotics particularly in view of the association of agranulocytosis with clozapine and of aplastic anaemia with remoxipride. The Committee on Safety of Medicines and Medicines Control Agency 'yellow card' post-marketing surveillance data were analysed for reports of haemopoietic disorders with the 16 antipsychotics in common use. Corrections for relative risk were made in three separate ways: (i) control for degree of use, using Northern Ireland prescribing data for 1995; (ii) percentage of total reports from 1963 to 1996; and (iii) examination of the first 5 years' post-marketing data only. After clozapine and remoxipride the highest risks of haemopoietic reactions appeared to be associated with the aliphatic phenothiazine derivatives thioridazine and chlorpromazine. There is therefore no evidence of any increased risk with high-potency drugs such as haloperidol or pimozide or with the newer drugs such as sulpiride or risperidone. Continued vigilance, however, is necessary as more new atypicals become available and begin to be widely prescribed.

Key words: atypical antipsychotics; haemopoietic reactions; post-marketing surveillance

Introduction

The risks of adverse haematological effects associated with antipsychotic drugs have been well publicized and have led to stringent monitoring requirements in the case of clozapine and withdrawal from the market in the case of remoxipride (Committee on Safety of Medicines, 1993; Kerwin, 1993; Atkin and Veys, 1994). However, although the existence of such risks is well-established, it remains difficult to estimate their true prevalence and, in particular, to reach well-founded conclusions about the relative safety of different compounds.

In this article, we review data available from the UK monitoring system [Medicines Control Agency (MCA) database or 'yellow card' system], which has been collecting information since 1963, consider the problems of its interpretation and try to put it into the context of international findings with particular emphasis on the atypical antipsychotics clozapine, sulpiride and risperidone. The number of adverse events reported to such a voluntary system will be influenced by a number of factors as discussed later. The methodological problems of pharmacovigilance in general and the interpretation of the MCA 'yellow card' database in particular have been extensively reviewed by Rawlins (1995). He identified three main difficulties: (1) reporting rates tend to be highest shortly after marketing; (2) under-reporting means that it is rare for more than 10 percent of serious reactions to be reported; and (3) bias in reporting generated by adverse professional or lay media attention to particular issues of safety. A particular example of this with respect to antipsychotics is in the reporting of the neuroleptic malignant syndrome, which is discussed more fully later. These and other limitations must be borne in mind in any attempt to interpret the data.

Problems in interpreting spontaneous adverse reaction data

The number of people exposed to a drug

One major problem in comparing safety data for a range of drugs, over a period of time, is the establishment of a reliable denominator. The information from the 'yellow card' scheme provided by the MCA is not routinely presented in the context of patient exposure, therefore other sources are required to give an idea of the relative exposure to each drug.

When considering relatively rare events, data must be collected for some time before meaningful figures emerge, and any changes in drug use during this period must therefore be taken into account.

Age of the drug

Prescribing doctors are probably most aware of the need to report problems with drugs recently introduced into the market, and effects of older drugs are likely to be under-reported (Kerwin, 1993). Moreover, reporting may also be affected by media interest or by published reports of particular cases. Thus, reporting rates as a whole may vary over time, and are likely to be higher for newer drugs than for those that are well-established.

Differences in patient populations

The licensed indications and clinical uses of antipsychotic agents vary considerably. Older neuroleptics are more likely to be used for general sedation in the elderly or for their anti-emetic properties than newer drugs with more limited indications. This may affect adverse event rates in two ways:

Table 1 Spontaneous adverse reaction reports of and fatalities from haemopoietic disorders associated with antipsychotic drugs received by the Committee on Safety of Medicines and Medicines Control Agency up to November 1996

Drug	Total haemopoietic disorders[a]	Agranulocytosis	Aplastic anaemia
Chlorpromazine	131 (34)	56 (27)	4 (2)
Clozapine	552 (4)	91 (2)	– –
Droperidol	2 –	– –	– –
Haloperidol	21 (1)	1 (1)	1 –
Loxapine	3 –	1 –	– –
Pimozide	9 –	– –	– –
Remoxipride	34 (1)	– –	5 (1)
Risperidone	29 (1)	– –	1 (1)
Sulpiride	16 –	2 –	– –
Thioridazine	84 (12)	24 (9)	1 –
Trifluoperazine	46 (7)	3 (2)	4 (2)
Flupenthixol	46 (1)	1	1
Fluphenazine	16 (4)	3 (2)	2 (1)
Fluspirilene	3 –	– –	– –
Pipothiazine	– –	– –	– –
Zuclopenthixol	7 –	– –	– –

Figures in parentheses are fatalities.
[a]Includes: platelet related disorders; stem cell disorders (including aplastic anaemia); miscellaneous anaemias; leukaemias; disorders with decreased white blood cells (including agranulocytosis); and disorders with increased white blood cells.

effects may be related to the underlying condition and, secondly, variations in use may mean that the patient populations differ in terms of age or sex which may, in turn, affect the risk of adverse effects, or their rate of being reported.

In the case of schizophrenia, for example, although it is widely accepted that antipsychotic drugs are associated with unwanted extrapyramidal effects, very similar movement disorders have been observed in untreated patients (Cunningham Owens *et al.*, 1982) suggesting that the neuroleptics alone may not be responsible for these effects although they may accelerate their onset or exacerbate them. Furthermore, while McCreadie *et al.* (1996) found involuntary movements in untreated elderly patients, they had not been seen in a population of younger, untreated patients (McCreadie and Ohaeri, 1994), which may exemplify changes in the susceptibility to drug effects with age.

Other factors

Crude reporting rates provide no information about the dose of drug used or the severity of the reactions reported. There is also difficulty in assessing the role of drug–drug interactions. The information provided by the MCA differentiates between reactions associated with single constituent and multiconstituent products (i.e. use of the active substance on its own or with other drugs). The adverse drug reaction database contains all information provided by the reporter on the original 'yellow card' and anonymous details of cases may be made available. However, for the purposes of this analysis, other factors such as other concomitant medication taken and the timing of the suspected reactions could not be taken into account since these are only available for individual cases.

Methods

Various methods can be used to reduce these difficulties. While it is impossible to establish an exact denominator, it is possible to estimate the relative numbers of patients exposed to a drug from commercially-available surveys of prescription numbers or unit sales. Comparison with incidence data from smaller, but completely defined, populations may also be a useful check that an appropriate denominator is being used.

The number of prescriptions written for antipsychotic agents in Northern Ireland in the course of one year (1995) has been used as a proxy to estimate the relative frequency of use in the

Table 2 Spontaneous adverse reaction reports of haemopoietic disorders associated with antipsychotic drugs received by the Committee on Safety of Medicines and Medicines Control Agency up to November 1996—correction for relative use

Drug	Prescriptions in N. Ireland 1995	Relative frequency of haemopoietic disorders[a]	Total reports 1963–1996	Haemopoietic disorders (%)
Chlorpromazine	39 109	3.03	829	15.80
Clozapine	351[b]	1413.43	1328	41.34
Droperidol	69	26.19	139	1.44
Haloperidol	12 768	1.49	573	3.66
Loxapine	88	30.81	47	6.38
Pimozide	909	8.95	148	6.08
Remoxipride[c]			140	24.29
Risperidone	6064	4.32	389	7.46
Sulpiride	3263	4.43	342	4.68
Thioridazine	6022	12.61	440	19.09
Trifluoperazine	10 739	3.87	606	7.59
Flupenthixol	4841	8.59	686	6.71
Fluphenazine	3297	4.39	484	3.31
Fluspirilene	95	28.54	205	1.46
Pipothiazine	158	0	31	0
Zuclopenthixol	2595	2.44	172	4.07

[a]Number of reports (from Table 1) corrected for relative use by dividing by the proportion of prescriptions in Northern Ireland for each drug, e.g. trifluoperazine = 11.88 percent of the total, therefore adjusted figure = 46/11.88 = 3.87.
[b]Total no. of patients (data from Clozaril Patient Monitoring Service).
[c]Remoxipride was withdrawn from general use in 1994. 1993 data gave a relative frequency of 6.53.

Table 3 Spontaneous adverse reaction reports of haemopoietic disorders associated with antipsychotic drugs received by the Committee on Safety of Medicines and Medicines Control Agency in the 5 years from the date of the first reported reaction: haemopoietic disorders as a percentage of total reactions

	Total reactions	Haemopoietic disorders	Fatalities[a]	Agranulocytosis	Aplastic anaemia
Typicals					
Chlorpromazine	283	7.8	**4.2**	4.2	**0.4**
Droperidol	17	—	—	—	—
Haloperidol	50	—	—	—	—
Loxapine	74	2.7	—	1.4	—
Pimozide	37	2.7	—	—	—
Thioridazine	99	16.2	**2.0**	4.0	—
Trifluoperazine	230	1.7	—	—	—
Atypicals					
Clozapine	1663	23.6	**0.2**	3.4	—
Remoxipride	236	14.4	**0.4**	—	**2.1**
Risperidone[b]	679	4.3	**0.1**	—	**0.1**
Sulpiride	233	1.3	—	—	—
Depots					
Flupenthixol	35	—	—	—	—
Fluphenazine	74	1.4	**1.4**	1.4	—
Fluspirilene	169	—	—	—	—
Pipothiazine	27	—	—	—	—
Zuclopenthixol	27	—	—	—	—

[a]Percentage fatalities from haemopoietic disorders.
[b]Data only available for 4 years.

UK. The Central Services Agency in Northern Ireland (which represents 3% of the UK population) has been recording 95 percent of all prescriptions on computer since 1966, and these data have been useful in monitoring both temporal and regional variations in psychotropic drug prescribing (King *et al.*, 1982). Nevertheless, figures for 1 year greatly underestimate the exposure to older drugs during the 30-year reporting period, since many of the newer compounds have only recently become available.

These Northern Ireland estimates of exposure were used to calculate a relative use fraction for each antipsychotic drug compared with the total of 16 antipsychotics prescribed. This fraction was then used to calculate a relative risk figure for the reported haemopoietic disorders (from Table 1) and shown in column 3 of Table 2. [For this study no general practice prescribing figures for clozapine were available since the Northern Ireland data are derived from prescriptions dispensed by community pharmacies, whereas clozapine can only be supplied from hospital pharmacies. The figure for clozapine in Table 2 was provided by The Clozaril Patient Monitoring Service (CPMS) and is the total number of patients receiving clozapine in the province in 1995, and it is therefore a real denominator.]

Another technique to make allowance for variations in the total reporting rate over time, is to compare the reporting rates for haematological events with that for the total number of events reported. This may compensate for the problem of underreporting of events associated with older drugs and of other variations in reporting rates. This second method was also employed (columns 4 and 5 of Table 2).

Finally, it is possible to examine the reactions reported only during the first 5 years of the drug being on the market to attempt to control for the 'age' of the drug. This method is not entirely free from non-specific sources of variation or bias. For example, interest in a 'new' adverse effect may cause an increase in case ascertainment and distort the figures. In particular, the neuroleptic malignant syndrome (NMS) was not reported in association with chlorpromazine between 1963 and 1968, whereas there were 25 reports in the following 26 years (1968–1994). Likewise with haloperidol there were no reports of NMS in the first 5 years (1964–1969) but a total of 65 between 1969 and 1994. Only one case of NMS was reported with sulpiride between 1983 and 1988, but a further seven were reported in the next 6 years to 1994. On the other hand, 13 cases were reported with risperidone during the first 3.5 years (November 1992–May 1996). It would seem that clinicians were re-alerted to this syndrome after a flurry of letters and subsequent reviews in the *British Journal of Psychiatry*, *British Medical Journal* and the *Lancet* between 1983 and 1987 (Caroff *et al.*, 1983; Cope, 1983; Bates and Courtenay-Evans, 1984; Kellam, 1987) and have been identifying it more readily since. Furthermore, with the oldest drugs, e.g. chlorpromazine, which was first introduced in the UK in 1954, these data beginning in 1963 do not capture the first 5 years of post-marketing experience.

Results

30-year UK safety data

Table 1 shows the numbers of reports made to the MCA between 1963 and 1996 relating to haematological problems associated with antipsychotic drugs (CSM, personal communication). In Table 2 these crude figures have been corrected in two ways: (i) to allow for amount of exposure by using Northern Ireland prescribing data for 1995 (the most recent available) (second column); and (ii) expressing haematological reports as a percentage of the total reports received by the CSM/MCA for each drug (fourth column). The high number of total reports associated with clozapine reflects the fact that the CPMS closely monitors all patients on the drug and all incidents, whether considered to be drug related or not, have been reported to the CSM/MCA.

Both methods of calculating relative risks highlight the haematological problems associated with clozapine. Using the prescribing data loxapine, droperidol and thioridazine appear to be the next highest in rank order. Among the depots, fluspirilene seems to have a high relative risk but this is probably a function of the low numbers involved, since there were only three reports of haematological reaction, none of which was fatal (Table 1). From the percentage of total reports, after clozapine, remoxipride, thioridazine and chlorpromazine have the next highest relative risks in rank order.

Agranulocytosis

Figures for agranulocytosis also identify the particular risks of chlorpromazine and thioridazine as well as clozapine, and the high mortalities associated with this complication in these drugs, ranging from 37.5 percent (thioridazine) or 48 percent (chlorpromazine) to 100 percent (haloperidol) (Table 1). The much lower mortality seen for clozapine-induced agranulocytosis (2.2%) is probably a function of the stringent monitoring requirements of the CPMS which increases early detection and treatment. Almost 11 000 patients had been treated with clozapine in the UK, up to November 1996, and there were two fatalities in a total of 91 cases of agranulocytosis, which gives a mortality rate of 2.2 percent (Novartis Pharmaceuticals, personal communication).

Aplastic anaemia

Aplastic anaemia appears to be far less common than leucocytopenias, but both are associated with chlorpromazine and trifluoperazine (Table 1). This is partly a function of the 'age' of these drugs since there was only one case associated with chlorpromazine and none with trifluoperazine during the first 5 years after marketing (Table 3). Interestingly, no cases of aplastic anaemia have been associated with clozapine. Conversely, remoxipride was linked to several cases of aplastic anaemia but none of agranulocytosis, suggesting different mechanisms of action for these two disorders.

5-year data

The total number of reactions reported for each antipsychotic during the first 5 post-marketing years are shown in Table 3 (CSM, personal communication). Risperidone has only been marketed in the UK since June 1993, although it was used in clinical trials before this date, therefore information is only available for a 4-year period (November 1992 to October 1996). Haematological reactions are expressed as a percentage of the total reactions reported to allow for variations between drugs in the number of reactions associated with individual reports. Once again, a similar picture emerges that after clozapine the highest risks are associated with thioridazine, remoxipride and chlorpromazine in that order. With regards to fatalities from haemopoietic disorders, chlorpromazine and thioridazine had the highest incidences, suggesting that agranulocytosis was not being recognized early during the 1960s. The low fatalities with clozapine presumably again reflects the effectiveness of the CPMS. The relatively low *percentage* of total reactions due to agranulocytosis associated with clozapine (3.4%) is probably a function of the 100 percent capture rate of all patients and the inclusive recording and reporting of *all* reactions by the CPMS. According to the manufacturer, data from countries in which the total patient exposure is accurately recorded show a consistent incidence of agranulocytosis of 0.8 percent in the first year of therapy reducing 10-fold in subsequent years to give a total cumulative incidence of the order of 1 percent (Novartis Pharmaceuticals, personal communication).

Discussion

As with all pharmacovigilance studies there are several limitations in this study. In particular, the use of Northern Ireland prescribing data to estimate the denominator for comparison with a UK-wide numerator for one of the estimates of relative risk (column 3, Table 2) is unsatisfactory, but was the best use of the available data, and was only used to attempt to refine the total raw data reported in Table 1. No attempt to estimate absolute or excess risk was made. It would be invalid only if the Northern Ireland prescribing patterns or risks of haematological adverse reactions were known to differ significantly from the rest of the UK. Of the 999 total reports of haematological reactions to the MCA up to November 1996, 19 (2%) were from Northern Ireland (18 for clozapine and 1 for remoxipride), suggesting relative under-reporting in the Province but a similar pattern of ascertainment.

Comparison with international data

International figures, especially those from the US, provide a larger population base than the UK and may help to establish reliable denominators. Epidemiological data derived from Medicaid provide the best available estimate of the background incidence of haematopoietic disorders in the general population. These indicate an incidence of neutropenia of 35.7 cases/million patients/year and of agranulocytosis of 7.2 cases/million patients/year (Strom *et al.*, 1992). In a population based case–control study of analgesic use conducted in Europe and Israel, the International Agranulocytosis and Aplastic Anaemia Study (1986) reported a lower background incidence of agranulocytosis of between 4.4 (community) and 6.2 (total hospital and community) cases/million using age- and sex-standardized region-specific rates.

Close monitoring and research provides more accurate figures for patients receiving clozapine, which indicate a greatly increased annual incidence of agranulocytosis of 8000/million patients (Alvir *et al.*, 1993). According to the manufacturer, however, between 1972 and 1995 900 000 *patient years of exposure* to clozapine worldwide have been associated with 1585 reports of neutropenia, 997 reports of agranulocytosis (1108 per million), 56 percent of whom were on concomitant medication, and 99 dyscrasia-related deaths (Novartis Pharmaceuticals, personal communication).

In the 2 years before its withdrawal in 1993, an estimated 56 000 patients had been treated with remoxipride worldwide. There were eight reports of aplastic anaemia (two of which were fatal), all involving concomitant medication, and so, although causality was not established it was considered prudent to withdraw the drug in view of this cluster of cases (personal communication, Awen Little, Astra Pharmaceuticals Ltd).

Although none has been reported in the UK, two cases of agranulocytosis have been reported in American patients receiving risperidone, where the cumulative exposure is now estimated to be approximately 0.5 million patients (Janssen Research Foundation, unpublished data). Based on the manufacturer's estimates of risperidone exposure, the annual incidence of neutropenia in patients receiving risperidone is similar to that seen in the general US population (31.4/million for risperidone compared with 35.7/million for the total population) while the reported incidence of agranulocytosis is actually lower (4.5/million compared with 7.2/million for the total). While calculations of cumulative exposure based on mean dosage and length of treatment and use of Medicaid data can only be considered best estimates, these figures indicate that the risk of haemopoietic disorders associated with risperidone, if any, is certainly several orders of magnitude less than that associated with clozapine. Three published case reports have also suggested that risperidone is a safe alternative after neutropenia induced either by typical antipsychotics (Mahmood *et al.*, 1996) or influenza (Bondolfi *et al.*, 1996).

Risk factors for developing haematological disorders

Most adverse events appear highly idiosyncratic and it is almost impossible to predict which patients are at greatest risk. Agranulocytosis associated with phenothiazines has been reported most often in white, elderly women, although this was initially thought to be a function of prescribing patterns (Edwards and Barnes, 1993). It is also reported more often during treatment with high doses and within the first 10 days (Pisciotta, 1971). Grohmann *et al.* (1989) monitored 13 000 antipsychotic treated inpatients from 1979–1988. In this only published prospective study seven cases of agranulocytosis were detected, all in women, one with clozapine and six with perazine (3 in combination with other drugs). The analyses also found significant leucopenia in an additional eight cases (3 in combination with other drugs). Thus women may be at higher risk of agranulocytosis, and polypharmacy may increase the risk of this and other blood dyscrasias.

More detailed data are available for clozapine, which also suggest that women may be at slightly higher risk than men of developing agranulocytosis (Krupp and Barnes, 1992; Alvir *et al.*, 1993). There is also a suggestion of genetic susceptibility and an association with the HLA-B38, -DR4, -DQw3 haplotype which has an increased incidence in Ashkenazi Jews (Yunis *et al.*, 1992). No HLA association has been found to account for the cases of agranulocytosis which occurred in Finland, although the Finns are genetically a fairly homogeneous population.

Since other antipsychotics are known to have haematological effects, patients receiving more than one drug are probably at greater risk than those receiving clozapine alone, but no specific combinations have been identified. Gerson and Meltzer have shown that carbamazepine may be directly toxic to marrow, and therefore discourage its use as a concomitant to clozapine (Gerson *et al.*, 1992).

Lithium, although not an antipsychotic, is widely used in bipolar or affective disorders and may be used in conjunction with neuroleptics. It is known to stimulate granulopoiesis and may induce leukocytosis. If used with clozapine, this could mask an underlying granulocytopenia and such patients should be carefully monitored, with particular attention paid to the differential leukocyte count (Adityanjee, 1995).

Mechanisms of action

Haematological effects may be caused by direct toxicity of the drug or its metabolite, or indirectly by an immunologically modulated mechanism. Chlorpromazine has been shown to have a directly toxic effect on granulocyte precursor cells causing a decrease in proliferative potential and in DNA synthesis (Gerson *et al.*, 1992). The presentation of chlorpromazine-associated dyscrasia supports this theory, since it tends to have a gradual onset and the time course is not accelerated on re-challenge (Uetrecht, 1992). Progression to agranulocytosis is relatively uncommon, and probably represents an asymptomatic condition which has persisted for some time (Pisciotta *et al.*, 1992).

In contrast, clozapine has not been shown to have any direct toxicity on cells *in vitro*, but it is not clear whether its effects are mediated by a metabolite, such as *N*-desmethyl clozapine (Gerson and Meltzer, 1992), a short-lived intermediate such as nitrenium ions formed in activated neutrophils (Uetrecht, 1992) or an immune-mediated response (Pisciotta *et al.*, 1992). Pisciotta *et al.* have demonstrated that a complement-dependent factor in serum from patients with clozapine-induced agranulocytosis can inhibit the activities of neutrophils *in vitro* (Pisciotta *et al.*, 1992). An immunological response is also suggested by Safferman's observation that patients re-challenged with clozapine (before the risks were fully understood) developed agranulocytosis more rapidly than when they first received the drug (Safferman *et al.*, 1992). These various proposed mechanisms have recently been reviewed by Pirmohamed and Park (1997). The target cells affected appear to be the myeloid precursors, although mature neutrophils may also be targeted simultaneously by the toxic nitrenium ion. However, whether this is directly toxic or acts as a hapten to initiate an immune reaction is still unresolved.

Remoxipride was withdrawn from sale shortly after haematological problems emerged and therefore has received less research attention. However, one report suggested that it was not directly cytotoxic to erythroid cells (Murphy *et al.*, 1994).

Conclusions

While the choice of antipsychotic treatment will depend on a number of factors, including efficacy and tolerability, haematological safety should also be considered. In view of the problems with clozapine and remoxipride there has been concern that blood dyscrasias may be a 'class effect' of new atypicals. However, after reviewing the available data, there is no evidence for this. In fact, it appears that the phenothiazine derivatives, chlorpromazine, thioridazine and trifluoperazine, are associated with an increased incidence of haemopoietic disorders and, in the case of chlorpromazine, this is probably due to direct toxicity on granulocyte precursor cells.

The piperazine phenothiazine fluphenazine and some of the older antipsychotics including the thioxanthenes (flupenthixol and zuclopenthixol), haloperidol and pimozide appear to be associated with less risk than the aliphatic phenothiazines. Of the newer, atypical agents, haematological problems do not appear to be associated with either risperidone or sulpiride. For the next generation of atypicals (sertindole, olanzapine, quetiapine, ziprasidone and zotepine) which have so far not been associated with significant haematological abnormalities in clinical trials, close post-marketing surveillance will be necessary to establish that they are equally safe.

Increased vigilance may lead to increased detection and reporting rates of adverse reactions and can distort comparisons with older drugs. Nevertheless, this is particularly important with severe life-threatening reactions such as haematological disorders and the neuroleptic malignant syndrome since the incidence of fatalities can be reduced by early detection as can be seen by the lower fatality rate with clozapine associated agranulocytosis compared with other antipsychotics, and the gradual reduction in NMS-associated fatalities in recent years.

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