Fatal toxicity of drugs used in the treatment of psychotic illnesses

NICHOLAS BUCKLEY and PETER McMANUS

Psychiatric illnesses such as schizophrenia and bipolar disorder are frequently treated, in the community, with medication. These illnesses carry a substantial risk of self-poisoning and suicide (Mortensen & Juel, 1993). One strategy to reduce deaths from self-poisoning is to identify the drugs which are more toxic in overdose than other drugs used for the same indication. The mechanism of toxicity of these drugs is unknown but is usually attributed to quinidine-like effects on the heart and effects on a variety of other receptors (muscarinic, histamine and alpha$_1$ adrenergic). There is no life-threatening toxicity attributable to effects on dopamine receptors. Therefore, it might be expected that low-potency drugs, which as a general rule are less selective for dopamine receptors, might have more severe effects in overdose through greater effects on other receptors. This is analogous to the greater sedative and anti-muscarinic effects observed with therapeutic use of low-potency antipsychotics. In overdose presentations to hospitals low-potency antipsychotics, such as thioridazine and chlorpromazine, have greater cardiotoxicity and sedative effect respectively than more potent antipsychotic drugs when taken in overdose (Buckley *et al*, 1995).

SELF-POISONING

As most overdose deaths occur out-of-hospital, it is important to compare drugs in terms of their fatal toxicity. This has previously been done for antidepressants and benzodiazepines by calculating a fatal toxicity index (FTI; Serfaty & Masterton, 1993; Henry *et al*, 1995). The number of fatal poisoning is divided by measures of drug usage to give a FTI of deaths per million prescriptions or deaths per million patient-years. Although it is implied in such studies that differences in FTIs are due to the inherent toxicity of the drugs when taken in overdose, a number of assumptions are made. It is not possible from coronial data to exclude the possibilities that drugs are more frequently taken, or are prescribed for or taken in overdose by an at-risk group (e.g. those with more severe psychiatric illnesses or cardiac disease). Subjects have a number of characteristics which may influence the choice of drug prescribed. The subject's characteristics also affect their risk of poisoning or their risk of death from poisoning. These characteristics include age, gender, other medical conditions, whether the drugs were prescribed for acute or chronic psychiatric illness or other indications and whether or not the drugs were given specifically to counteract suicidal behaviour. Further, the perceived risk of overdose with each drug has the potential to confound the relationship with fatal toxicity. This has been observed with antidepressants, where safer drugs are preferentially prescribed to subjects at higher risk of poisoning and suicide (Isaacson *et al*, 1994), but is unlikely to affect antipsychotics as there have been no previous studies. The FTIs have also been criticised for using prescriptions rather than the number of people using the drug (Kelleher *et al*, 1992).

The coroner's recording of cause of death may not always be accurate from a toxicological perspective. When Dwyer & Jones (1984) examined the problem of dextropropoxyphene poisoning by auditing coroner's files, they found about a third of deaths from dextropropoxyphene had been missed or classified as dextropropoxyphene/paracetamol combination overdoses. However, it should be remembered that inacurracy in measurement of outcomes reduces differences observed between exposures. Unless a plausible bias can be postulated such inaccuracy would not explain the observed differences between drugs. Despite these limitations of FTIs, such estimates of the relative toxicity in overdose of drugs are the best means we have of comparing fatal toxicity in human overdose.

Calculating a FTI for antipsychotics

We examined the fatal toxicity of antipsychotic drugs and anticholinergic drugs for the years 1983–1992. The number of deaths in England and Wales due to acute poisoning by a single drug alone with or without alcohol co-ingestion was obtained from the Office of Population Censuses and Surveys (1994). Fatal poisonings due to multiple drugs (about 30–40% of the total) are excluded. There were no fatal poisonings from the use of fluspirilene, droperidol or pipothiazine which are generally administered parentally while clozapine was listed as having caused one death despite there being no prescriptions issued.

The number of prescriptions for England was used as a measure of relative drug usage. The data was supplied by the Statistics Division of the Department of Health for the years 1983–1992. The data for the years 1983–1990 were obtained from a survey of 1 in 200 prescriptions dispensed by community pharmacists and appliance contractors only. However, data from 1991 to 1992 covered all prescriptions dispensed by community pharmacists, appliance contractors, dispensing doctors and prescriptions submitted by prescribing doctors for items personally administered.

An FTI, expressed as deaths per million prescriptions, was calculated by dividing the number of deaths in England and Wales by the prescriptions (in England alone) for the years 1983–1992. Ninety-five per cent confidence intervals were calculated by assuming the prescriptions (i.e. the denominator of the FTI) were fixed and that the deaths followed a Poisson distribution. The 95% confidence limits were obtained for the deaths from a table of exact confidence intervals for a Poisson distribution (Lentner, 1984). These limits were divided by the prescription count to obtain the lower and upper confidence limits for the fatal toxicity index. Drugs are listed in descending order of the fatal toxicity index.

We also calculated the number of deaths per million years of patient use for each drug for the years 1983 to 1992. We used data on deaths from England, Wales and Scotland (from the General Registrars Office). Comparable death data were not available from Northern Ireland which is 3.4% of the total UK pharmaceutical market. Data on the total pack sales of tablet and capsule formulations in the UK for these years were obtained from Intercontinental Medical Statistics (1983–1992).

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The total volume of each drug sold was divided by the defined daily dose for that drug to determine the number of patient-years of each drug sold. The defined daily dose, a World Health Organization (1994) approved measure of drug utilisation, represents the assumed daily dose of the drug when used for its main indication in adults. Drugs sold as syrups or parenteral preparations were excluded as these preparations are not usually self-administered and are rarely involved in deliberate self-poisoning. The defined daily dose data were converted to patient-years of use data by assuming that the defined daily dose represented the average prescribed dose for each drug. Permission to publish the aggregate data on drug usage was requested but has to date not been granted. Thus, this FTI (deaths per million patient-years) is used only to examine the correlation with the standard FTI (deaths per million prescriptions).

To explore our hypothesis that potency would influence the FTI, Poisson regression was used to examine for associations between the K_d at D_2 receptors and the defined daily dose of each drug (where this was known) and the deaths per million prescriptions. The defined daily dose is inversely related to the dopamine blocking potency of antipsychotics (Richelson, 1994) and was used as not all antipsychotics had direct measures of D_2 binding.

Differences in the FTI of antipsychotics

We observed large differences in fatal toxicity in overdose between different drugs used in the treatment of psychotic illness. As suspected, low potency drugs generally had higher FTIs, although there were notable exceptions (Table 1). Pimozide had the lowest FTI (0, 95% CI 0–6.5), which is in contrast with the warnings published by the Committee of Safety in Medicines in 1990 and 1995 of the risk of sudden death with therapeutic use. Presumably these deaths were not included as poisoning deaths but it suggests some caution should be used in interpreting this FTI. Loxapine, although rarely prescribed, had the highest estimated fatal toxicity index but the 95% CI is very wide. This is intriguing as amoxapine has the highest fatal toxicity index of all the antidepressants (Henry *et al*, 1995), and is the desmethyl metabolite of loxapine. Both of these drugs frequently cause seizures in overdose (Ellenhorn, 1997). These drugs are also known to be potent antagonists at $GABA_A$ receptors (Squires & Saederup, 1993), a likely explanation for both their pronounced proconvulsant effect and high fatal toxicity. There are many other drugs in which the observed toxicity is low, however, the upper confidence limit is very high. This is a reflection of the infrequency with which these drugs were used over the 10 years studied and no conclusions can be drawn about the fatal toxicity of these drugs. For drugs whose use is increasing, particularly the atypical antipsychotics, further comparisons should be made when more data are available.

Using Poisson regression there was a significant relationship between the FTI of the typical antipsychotic agents and both their potency at D_2 receptors ($P=0.0001$) and their defined daily dose ($P<0.0001$). This is illustrated for those drugs with reasonably narrow CIs (>100 000 prescriptions) in Figs 1 & 2. There was a good correlation between deaths per million prescriptions and deaths per million patient-years (Fig. 3) suggesting that the ranking of antipsychotic drugs in fatal toxicity is largely independent of the method of calculation.

Table 1 Fatal toxicity indices for antipsychotic drugs

	Deaths	Prescriptions (thousands)	Deaths per million prescriptions	95% CI
Loxapine	2	18	111.1	13.5–401
Remoxipride	1	12	86.2	2.2–480
Chlorpromazine	137	5595	24.5	20.6–28.9
Zuclopenthixol	2	132	15.2	1.8–54.9
Fluphenazine	2	180	11.1	1.3–40.2
Thioridazine	50	7623	6.6	4.9–8.6
Tetrabenazine	1	159	6.3	0.2–35.0
Trifluoperazine	23	4874	4.7	3.0–7.1
Promazine	3	1021	2.9	0.6–8.6
Haloperidol	5	2011	2.5	0.8–5.8
Sulpiride	1	498	2	0.1–11.2
Perphenazine	1	561	1.8	0–99
Flupenthixol	3	3337	0.9	0.2–2.6
Trifluperidol	0	3	0	0–1419
Chlorprothixene	0	8	0	0–473
Thiopropazate	0	10	0	0–384
Methotrimeprazine	0	18	0	0–207
Oxypertine	0	33	0	0–111
Benperidol	0	54	0	0–67.9
Droperidol	0	67	0	0–54.9
Pericyazine	0	181	0	0–20.4
Pimozide	0	569	0	0–6.5
Total	231	26 962	8.6	7.5–9.8

FTI as an influence on the prescription of antipsychotic drugs

Based on this FTI, as well as clinical studies of adverse effects in therapeutic use and toxicity in overdose (Buckley *et al*, 1995), it could be argued that some high potency antipsychotic drugs have advantages in terms of their safety profile. However, the use of high potency drugs often requires co-administration of an anticholinergic agent to treat extrapyramidal side-effects. The choice of anticholinergic drug added is important as the fatal toxicity index of orphenadrine was higher than that of all but one of the antipsychotic drugs and orphenadrine was the single most common cause of death of all drugs analysed (Table 2). Orphenadrine has pronounced toxicity in overdose causing seizures and cardiac arrhythmias (Ellenhorn, 1997). As there are other drugs with much lower toxicity, such as benztropine and benzhexol, and no clear advantages of orphenadrine, routine use of orphenadrine should be avoided. It is

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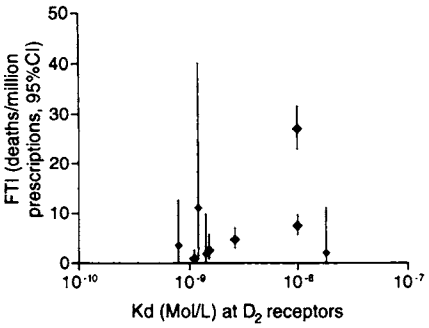

Fig. 1 Correlation between fatal toxicity index (FTI) of antipsychotic drugs and dopamine (D_2) blocking potency. ◆, >1 000 000 prescriptions; ◆, 100 000–1 000 000 prescriptions; —, 95% CIs, P=0.0001.

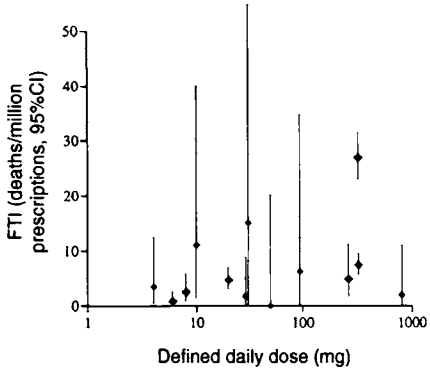

Fig. 2 Correlation between FTI of antipsychotic drugs and the defined daily dose; ◆, >1 000 000 prescriptions; ◆, 100 000–1 000 000 prescriptions; — 95% CIs, $P<0.0001$.

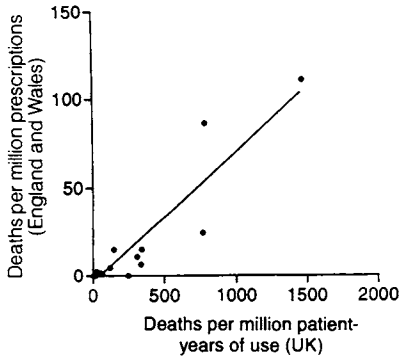

Fig. 3 Correlation between FTIs for antipsychotic drugs calculcated by deaths per million prescriptions and deaths per million patient-years (r^2=0.85).

Table 2 Fatal toxicity indices for anticholinergic drugs

	Deaths	Prescriptions (thousands)	Deaths per million prescriptions	95% CI
Orphenadrine	166	2320	71.5	61.1–83.3
Procyclidine	26	4259	6.1	4.0–8.9
Benzhexol	3	2199	1.4	0.3–4.0
Biperiden	0	14	0	0–267.3
Methixene	0	131	0	0–28.1
Benztropine	0	288	0	0–12.8
Total	195	9211	21.2	18.3–24.4

Data on prescriptions are for England only and are from the Prescription Costs Analysis system. The data up to 1990 are not consistent with the data from 1991 onwards. Values in the tables may not add up to the total because of rounding.

possible that a number of these deaths were related to substance misuse. The misuse potential of anticholinergic drugs is another reason for choosing an anticholinergic with a large margin of safety.

There are many factors other than toxicity in overdose that may influence the prescribing of antipsychotic drugs. The FTI of the most toxic of these drugs suggests they will cause death from poisoning around one in every thousand patient-years of use. Any other fatal adverse drug reaction with this frequency would be likely to lead to withdrawal of the drug from the market. However, a change from prescribing the most toxic to the least toxic drugs is likely to have only a small impact on suicide rates in this patient group, as poisoning accounts for only about 20% of suicides. An unknown proportion of these poisonings are due to this group of drugs. Thus, the potential reduction in suicide, assuming that treatments are equally efficacious, would be in the order of 5–10%. Sedative effects of some low-potency drugs, in particular chlorpromazine, are often used to treat agitated acutely psychotic subjects. Effective treatment of psychotic symptoms is an important factor in the prevention of suicide and these data do not suggest that subjects who have a particular requirement for a sedative antipsychotic or who are satisfactorily controlled on a particular medication should be changed to alternative medication. The choice of first-line treatment should include consideration of the fatal toxicity.

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