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Comment

The Toxicity of Antidepressants

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Considerable attention has been paid, both by regulatory authorities and clinicians, to the side-effects of antidepressants, but despite the known high suicide risk in depression, toxicity in overdosage has been largely ignored. On the basis of the evidence currently available, 'older' antidepressants appear to be more toxic than 'newer' agents. A case can be made for limiting the use of some of the older tricyclic antidepressants, especially in patients who remain in the community, when continuous supervision is lacking, in favour of newer, safer drugs.

It is now 30 years since 'antidepressants' as presently understood were introduced. Following the discovery of imipramine, many similar compounds were developed. Around the mid-1970s, compounds having very different chemical structures but similar antidepressant effects emerged from pharmaceutical research.

Attention has focused upon four aspects of the activity of antidepressants: clinical efficacy, speed of onset of action, side-effect profile, and toxicity in overdosage. Available evidence suggests that over the whole spectrum of depressive illness there is no marked clinical superiority of any one antidepressant over another, nor is there evidence of differences of efficacy in respect of selective actions on individual neurotransmitter systems. Similarly, claims for a speedier onset of action for any particular antidepressant have not been substantiated. There is, however, evidence that antidepressants differ considerably in their side-effect profiles and in their toxicity.

Much attention has been paid in recent years, especially by regulatory authorities, to rare, idiosyncratic, often life-threatening adverse reactions. Such considerations led, for example, to the withdrawal of zimeldine and nomifensine, and to the issue of warnings regarding the need for regular monitoring of patients receiving mianserin.

By contrast, toxicity in overdosage has received much less attention, despite the acknowledged potentially high suicide risk in depression, and this crucially important aspect has been virtually ignored at the regulatory level.

Self-poisoning and antidepressants

Depression is the disorder most commonly associated with deliberate self-poisoning (Weissmann, 1974; Newsom-Smith & Hirsch, 1979; Urwin & Gibbons, 1979). Poisoning is the most common means of suicide in the UK, accounting for 54% of female and 25% of male suicides (Bulusu & Alderson, 1984); the medicinal drugs that have been most frequently used are analgesics, barbiturates, tranquillisers, and antidepressants (Farmer, 1986). About two-thirds of those individuals who successfully commit suicide have visited their family doctor in the previous month, and 40% in the previous week (Robins *et al*, 1959; Barraclough *et al*, 1974).

Toxic effects of antidepressants in overdosage

Although there are individual differences, the characteristic clinical picture of serious tricyclic antidepressant overdose is one of coma, seizures, hypotension, conduction delay, as demonstrated in the electrocardiogram, and ventricular dysrhythmias (Kulig, 1986). Complications can include a wide variety of arrhythmias – sinus tachycardia, premature ventricular beats, ventricular tachycardia or sade de pointes, ventricular bradycardia, and ventricular fibrillation, and these are important causes of death (Pentel, 1986). Patients who have overdosed with tricyclic antidepressants may therefore require very intensive care. However, not commonly acknowledged is the fact that some 70–80% of individuals who take tricyclic antidepressant overdoses do not reach hospital alive (Callahan & Kassel, 1985; Crome & Newman, 1979; Boldy, 1985). Of the newer 'tricyclic' compounds, maprotiline appears to be pharmacologically and toxicologically similar to its conventional forbears, (Kulig, 1986; Crome & Ali, 1986), whereas the information so far available suggests that lofepramine is much less toxic (Crome & Ali, 1986; E. Merck Ltd, 1987, personal communication).

Of the novel antidepressants, overdoses of both mianserin (Crome & Ali, 1986) and trazodone (Kulig, 1986; Crome & Ali, 1986; Hassan & Miller, 1985) may cause drowsiness, but neither is associated with convulsions or ECG abnormalities. While data on

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overdosage with 5HT reuptake inhibitors such as fluoxetine and fluvoxamine are limited, experience so far suggests that these agents lack the severe toxicity of the tricyclics (Crome & Newman, 1979).

Toxicity in overdosage

In animals, fatal toxicity of a drug is expressed in terms of the LD_{50}, the dose required to kill 50% of animals on test. Obviously there can be no direct relationship to humans, but nevertheless extrapolation from animal studies has been attempted.

The most common measure in humans is the 'therapeutic index', defined as the ratio of the dose at which there is no more than 5% toxicity to the dose at which there are at least 95% cures. This index has little value in predicting 'fatal' toxicity, but the concept, however, has been used by Girdwood (1974) to determine the fatal toxicity of certain drugs. He defined an index of toxicity as the ratio of the number of deaths reported annually to the number of prescriptions issued per year. A similar index was used by Barraclough (1974) to examine deaths associated with hypnotic drugs. This index has now been extended to cover a wide range of drugs. The index of toxicity is defined as:

$$T = \frac{\text{Number of deaths associated with drug}}{\text{Number of prescriptions for drug}}$$

It can be normalised such that the value of T for quinalbarbitone is 100.

King & Moffat (1983), using statistics for drug-associated deaths taken from the Office Populations Censuses and Surveys (OPCS) mortality tables for 1976 to 1978, devised a table of the indices of fatal toxicity for 47 drugs commonly encountered in self-poisonings. An entry was made for each drug according to the number of deaths with which it was associated, regardless of whether the death was attributed to accident, suicide, or otherwise. For multiple drug consumption, entries were made for each drug named. Prescription statistics for the period were provided by the Statistics and Research Division of the Department of Health and Social Security, and excluded prescriptions given in hospital. Mortality statistics referred to England and Wales, whereas prescription statistics referred to England only. Their consideration, however, was considered to be valid.

Compared with a value of 100 for quinalbarbitone, the T values for tricyclic antidepressants commonly encountered in human poisoning were amitriptyline 11.5, doxepin 11.3, dothiepin 11.1, trimipramine 10.1, imipramine 9.2, clomipramine 6.1, and nortriptyline 5.0.

King & Moffat (1983) state that, as with barbiturates, values for antidepressants provide evidence that T is related to P, the n-octanol/water partition coefficient, and they consider that the lower toxicity of nortriptyline (5.0) compared with amitriptyline (11.5) is in keeping with the general rule that a metabolite is more soluble in water and less toxic than its parent.

Leonard (1986) suggested that the concern of UK health authorities with the side-effects of the antidepressants nomifensine and mianserin detracted from an ever-more serious aspect of drug toxicity, which he considered had been largely ignored, namely the incidence of antidepressant-induced fatalities.

Since suicidal thoughts and attempts are common in depression, in providing depressed patients with drugs such as the older tricyclic antidepressants that are lethal in overdosage, the clinician was almost "willing the patient to succeed," he claimed.

Leonard (1986) argued not for complacency about the rare occurrence of haemolytic anaemia and agranulocytosis after the administration of therapeutic doses of nomifensine and mianserin, but rather for a more realistic attitude to deaths from self-inflicted or accidental overdosage.

The number of deaths, both intentional and accidental, for various antidepressant drugs for the period 1977–83 for England and Wales was tabulated using OPCS data. When only one drug was taken, the numbers were: amitriptyline 750, dothiepin 376, imipramine 180, trimipramine 101, doxepin 59, maprotiline 58, clomipramine 30, and mianserin 23. When several drugs were taken, antidepressants were implicated as follows: amitriptyline 391, dothiepin 120, imipramine 91, trimipramine 76, mianserin 40, doxepin 37, clomipramine 31, and maprotiline 20.

Such figures however take no account of the frequency of use. Leonard (1986) noted that it was not possible accurately to calculate the number of deaths per million patients treated with the individual drugs, because figures for total numbers of patients treated, duration of treatment, and dose are not available. Nevertheless, assuming an average daily dose of 112 mg for 60 days for tricyclic antidepressants and 45 mg for 60 days for mianserin, it was possible to calculate an estimated death rate per million patients treated, for each antidepressant. The rates were amitriptyline 166, dothiepin 147, maprotiline 115, imipramine 105, doxepin 99, trimipramine 93, clomipramine 34, and mianserin 15.

Leonard (1986) suggested that the general issue of antidepressant safety should be taken into account when regulatory authorities issue warnings about potentially serious side-effects of new antidepressants.

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In his view, the incidence of such side-effects should be compared with that for older drugs, so that clinicians can make a realistic assessment.

An example of a newer, but nevertheless tricyclic antidepressant with an apparently very different toxicity profile is lofepramine. Up to 31 March 1987, the estimated number of patients treated with this drug world-wide was 1 017 666, with no known case of death through gross ingestion (E. Merck Ltd, 1987, personal communication).

Montgomery (1987, unpubl.) also estimated that fatalities from overdosage with tricyclic antidepressants ranged between 100 and 150 per million patients treated, whereas the rate for mianserin was only 13. He estimated that deaths from blood dyscrasias in patients receiving mianserin were only at the rate of between 2 and 4 per million patients treated. The incidence of rare side-effects, such as the peripheral neuropathy seen with zimeldine, was about 8 per million. Older tricyclic antidepressants were associated with more deaths than the newer antidepressants, and he felt that clinicians should include this data in their risk–benefit analysis.

It is difficult to obtain data from elsewhere in the world regarding the relationship between deaths from antidepressant overdosage and the volume of prescriptions issued. The dangers of tricyclic overdosage are however well recognised. In the United States, for example, in 1982, it was the third most common cause of drug-related death after alcohol-drug combinations and heroin (Callahan & Kassel, 1985). Cassidy & Henry (1987) calculated a fatal toxicity index on the basis of deaths per million National Health Service prescriptions issued for antidepressants during the years 1975–84 in England, Wales and Scotland. They also calculated indices for the number of standard units and gross quantities of drugs prescribed. All three methods produced similar rankings for the drugs concerned. Cassidy and Henry found that the fatal toxicity index (number of deaths per million prescriptions) for all antidepressants was 34.9. But when drugs introduced before 1970 (essentially tricyclic antidepressants) were compared with those introduced since 1973, there were highly statistically significant differences (with the exception of maprotiline).

The number of fatal poisonings observed and the numbers expected (in parenthesis) for pre-1970 antidepressants were dibenzepin 4 (0.9), desipramine 13 (5.7), dothiepin 533 (372), amitriptyline 1181 (886), nortriptyline 57 (51), doxepin 102 (114), imipramine 278 (342), trimipramine 155 (196), opipramol 2 (3.2), clomipramine 51 (160), protriptyline 6 (20), and iprindole 2 (8.9). The fatal toxicity indices (deaths per million prescriptions) were dibenzepin 157.5, desipramine 80.2, dothiepin 50.0, amitriptyline 46.5, nortriptyline 39.2, doxepin 31.3, imipramine 28.4, trimipramine 27.6, opipramol 21.8, clomipramine 11.1, protriptyline 10.3, and iprindole 7.8.

Similar calculations for deaths observed and expected from the monoamine oxidase inhibitors were tranylcypromine 15 (9), phenelzine 24 (36.7), isocarboxazid 3 (8.2), and iproniazid 0 (0.97).

With the exception of maprotiline, the results for antidepressants introduced since 1973 were very different from those of the tricyclic antidepressants. The deaths observed and expected were maprotiline 83 (77), trazodone 6 (15), viloxazine 2 (7.4), butriptyline 1 (4.7), mianserin 30 (187), nomifensine 3 (42), and lofepramine 0 (3.7). The fatal toxicity indices were maprotiline 37.6, trazodone 13.6, viloxazine 9.4, butriptyline 7.5, mianserin 5.6, nomifensine 2.5, and lofepramine 0 (3.7). Subsequent calculations on more data showed that the fatal toxicity index for lofepramine should be 0.0 (Henry, 1987, personal communication).

Cassidy & Henry (1987) accepted some of the limitations of their data. They acknowledged that there is an assumption that the number of prescriptions issued is a reliable indicator of the availability of the drug in the community. The prescription data were derived from National Health Service prescriptions issued by general practitioners, who may see a selected population of depressed patients. Nevertheless, they believe that their fatal toxicity index is a "useful means of estimating the relative danger or safety of antidepressants". It is acknowledged that the index may be biased by systematic errors in mortality data or prescription data, and by the fact that death was actually due to drug ingestion cannot always be confirmed. When prescribing, the choice of drugs given to patients recognised to be suicidal may be determined by certain assumptions of safety. Some antidepressants may be prescribed for conditions other than depression such as enuresis.

The indices calculated by King & Moffat (1983), Barraclough (1974) and Girdwood (1974) all included deaths due to more than one drug. For this reason their fatal toxicity indices are higher and perhaps less accurate. When recalculated, including only deaths due to one drug alone, for a representative series of antidepressants, the differences for most drugs diminish.

The fact that amitriptyline has been implicated in roughly half of the deaths attributed to tricyclic antidepressants in their own study and in others in the UK and United States is noted by Cassidy & Henry (1987). They point out that:

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"When prescribing antidepressant drugs the doctor usually considers the toxic risks from self poisoning as well as from adverse effects. Regulatory authorities, however, tend to grant licences not on the toxicity of drugs in overdose but on their safety in therapeutic use . . . overall morbidity and mortality related to the drugs could be considered by regulatory authorities when a drug comes up for renewal of licence . . . serious consideration should be given to preferentially prescribing the newer drugs, especially to patients who are considered at particular risk of suicide by ingestion of an overdose of their medication."

Cassidy & Henry's (1987) data reveal some unexpected findings. For example desipramine, contrary to clinical impressions, appears to be more toxic than amitriptyline. Chemically similar drugs such as desipramine, dothiepin, doxepin, and clomipramine seem to have very different toxicities.

Fatal toxicity of antidepressants has been principally attributed to membrane-stabilising activity. The findings for desipramine, Cassidy & Henry, (1987) suggest, may be partially explained by the demonstration that *in vitro* it is a more potent membrane-stabilising agent than imipramine. An additional reason may be that it has been shown to cause seizures in overdosage more often than other tricyclics. Desipramine is rarely a first choice of drug with general practitioners. It may be that its very limited use is reserved for second choice of treatment of 'difficult patients'. Prescribing habits may perhaps also explain the apparent anomalies relating to doxepin and clomipramine, which have similar membrane-stabilising activity to that of other tricyclic antidepressants. Doxepin has been promoted for "the treatment of patients with a wide range of psychoneurotic disorders where anxiety and/or depression are prominent symptoms," and emphasis in the promotion of clomipramine has been placed on the treatment of phobic and obsessional disorders. Patients who have such disorders may be less likely to overdose than pure depressives.

Cost of care

Most of the information regarding morbidity and mortality resulting from antidepressant overdosage comes from the UK. Despite the acknowledgement that tricyclic overdoses are common, difficult to manage, and often lethal, a determined effort to obtain information from overseas produced very disappointing results. This was mainly due to the fact that in other countries there is no equivalent of the OPCS. It is therefore difficult to obtain reliable estimates about the size of the problem world-wide, and even more difficult to obtain information about the costs of tricyclic overdosage.

The Department of Health and Social Security in the UK provided some valuable information about cost incurred on patients poisoned by psychotropic agents – a wider group than just antidepressants (Department of Health & Social Security, 1986, personal communication). In 1982 there were 30 540 deaths and discharges from hospital from poisoning from psychotropic agents. The mean length of stay in hospital for this group was two days, making the hospital days 61 080. At 1985/86 prices the cost per in-patient day in an acute hospital of over 300 beds was about £99. Assuming that the number of deaths and discharges for psychotropic drug overdosage remained fairly constant from 1982 to 1985/86, the total cost to the health service of poisoning due to psychotropic agents would be £6 million at 1985/86 prices. Certain caveats apply when interpreting these figures. Costs vary from hospital to hospital, and in calculating them the assumption is made that most overdoses are treated at large general hospitals. The costs are based on average in-patient days and do not specifically relate to the in-patient days of overdose patients. Finally, the term 'poisoning' as far as official statistics are concerned covers more than just overdose, including for example 'side-effect'. The figure of £6 million of course does not reflect the cost of general practitioner services or incapacity following discharge, nor does it reflect the economic 'costs' in lost working hours, benefits paid, etc.

Conclusion

Available evidence suggests that toxicity in overdosage varies considerably between 'newer' and 'older' antidepressants. It is a much more likely cause of death than idiosyncratic side-effects. Yet drugs have been withdrawn from use for the latter reason but not for the former. It is difficult to understand the attitudes that have led to this state of affairs. Since a number of antidepressants are now available that have been shown to be equally efficacious, and to possess a similar onset of action, but to be appreciably less toxic, the continued widespread use of drugs like amitriptyline and dothiepin would seem questionable; if these drugs are to be used at all, such use should be restricted and strictly monitored. In order to reduce unnecessary mortality, depressed patients who remain in the community should be given newer, safer antidepressants.

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