Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data

Nicholas A Buckley, Peter R McManus

Several studies over the past 15 years have compared the number of fatal poisonings due to antidepressant drugs in the United Kingdom with drug use statistics to derive a fatal toxicity index: deaths per million prescriptions.12 Greater than 10-fold differences in the index have been shown between tricyclic antidepressants and even larger differences between some tricyclics and newer antidepressants. Explanations have focused on preference for noradrenaline or serotonin reuptake blockade, although only weak correlations have been observed3 and the explanation is toxicologically implausible.1 In the late 1990s the use of newer serotoninergic antidepressants increased dramatically. Some data show that venlafaxine in particular may not be as safe in overdose as other serotonergic drugs, with reports of deaths, arrhythmias, and seizures.1 We aimed to establish the relative frequency with which venlafaxine and other new antidepressants result in fatal poisoning.

Methods and results

We obtained the number of deaths in Scotland, England, and Wales due to acute poisoning by a single drug, with or without co-ingestion of alcohol, from the General Register Office for Scotland and the Office for National Statistics for the years 1993-9. We used the number of prescription items for England, Wales, and Scotland supplied by the respective departments of health for these years as a measure of relative drug use. Use in hospital is not included, but prescribing of antidepressants overwhelmingly occurs in general practice. For each drug we calculated a fatal toxicity index expressed as deaths per million prescriptions. We calculated the lower and upper 95% confidence limits for the index by using exact confidence intervals for the deaths.

The table lists the drugs in descending order of fatal toxicity index within British National Formulary drug classes. The serotoninergic drug class overall had a much lower index than the tricyclic antidepressants and monoamine oxidase inhibitors, but venlafaxine had a higher index than the individual and combined results of other serotoninergic drugs.

Comment

The most striking new observation is that the fatal toxicity index for venlafaxine is higher than those for other serotoninergic antidepressants and similar to those for some less toxic tricyclic antidepressants. This raises the question of whether venlafaxine should continue to be a first line drug in patients with suicidal ideation. Our results also confirm previously reported large differences in fatal toxicity index between other antidepressant drugs.12 This sort of analysis is open to several criticisms.1 Using the fatal toxicity index as a measure of lethality in overdose makes some assumptions, including that mortality data are not influenced by previous literature and that drugs are taken in overdose with similar frequency and in similar amounts. The perceived risk of overdose has the potential to confound by altering several variables. For example, “less toxic” drugs may be preferentially prescribed to patients at higher risk of poisoning and suicide,1 but they are also less likely to be listed as the sole cause of death from overdose.

Toxicity in overdose should be an important consideration in the choice of first line treatment but should be based on data for each individual drug and not on the therapeutic class or on measures such as serotonin or noradrenaline selectivity that do not directly lead to toxicity in overdose. Poisoning with antidepressants accounts for only about 4-7% of all suicides, but the proportion of suicides from antide-
Leflunomide can potentiate the anticoagulant effect of warfarin

V Lim, I Pande

Leflunomide (Arava; Aventis Pharma) is used widely to treat inflammatory arthritis. We report a case of a probable interaction between leflunomide and warfarin.

A 49 year old man with resistant rheumatoid arthritis started taking leflunomide at the recommended loading dose of 100 mg daily for three days. His international normalised ratio had been stable for a year while he was taking warfarin, and two days before starting treatment with leflunomide it was 3.4. After he took the second dose of leflunomide, he developed gross haematuria, for which he required hospital admission. His international normalised ratio had risen to 11, and warfarin was discontinued. His haemoglobin concentration was satisfactory and the normal range. A rechallenge was not possible or ethical.

Leflunomide was considered to have caused the increase in the patient's international normalised ratio. Such a role for leflunomide is supported by the temporal relationship to the abnormal ratio and the subsequent lower ratio had been stable for a year while he was taking warfarin.

The first information booklet for healthcare professionals on leflunomide implied that it was metabolised by cytochrome P-4502C9 and its effects may be increased, rather than decreased, by warfarin. This was contrary to the pharmacokinetics, according to the summary of product characteristics for Arava.

Funding: None.

Competing interests: None declared.