Relative toxicity of benzodiazepines in overdose

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See pp 215, 221, and editorial by Edwards

Abstract

***Objective*—To assess the sedative effects in overdose of temazepam and oxazepam compared with other benzodiazepines to determine if this explains reported differences in fatal toxicity.**

***Design*—Cohort study of patients admitted with benzodiazepine poisoning.**

***Setting*—Newcastle, Australia.**

***Subjects*—303 patients who had ingested benzodiazepine alone or in combination with alcohol and presented to a general hospital which served a well defined geographical area.**

***Main outcome measures*—Degree of sedation: Glasgow coma score, McCarron Score, and whether patients were stuporose or comatose.**

***Results*—Oxazepam produced less and temazepam more sedation than other benzodiazepines. Unadjusted odds ratios for coma with oxazepam and temazepam compared with other benzodiazepines were 0·0 (95% confidence interval 0·0 to 0·85) and 1·86 (0·68 to 4·77) respectively, $\chi^2=7·08$, 2df, P=0·03. After adjustment for potentially confounding effects of age, dose ingested, and coingestion of alcohol, the odds ratios were 0·22 (0·0 to 1·43) for oxazepam and 1·94 (0·57 to 6·23) for temazepam. Similar results were obtained for other measures of sedation.**

***Conclusions*—These results were in accordance with fatal toxicity indices derived from coroners' data on mortality and rates of prescription. The relative safety of benzodiazepines in overdose should be a consideration when they are prescribed.**

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Introduction

Benzodiazepines are generally thought to be safe in overdose.[1,2] Death after admission is rare and due to respiratory depression with aspiration of gastric contents.[2] Over 10 years in the United Kingdom, however, 1512 fatal poisonings have been attributed to benzodiazepines with or without alcohol.[3] These were compared with prescription data to establish a fatal toxicity index (deaths per million prescriptions) for each benzodiazepine. Similar indices have been derived for antidepressants[4] and barbiturates.[5] There were clear differences between benzodiazepines. Of drugs frequently prescribed, temazepam had the highest number of deaths per million prescriptions at 11·9 (95% confidence interval 10·9 to 12·8); above that of some tricyclic antidepressants.[3,4] In contrast, oxazepam had an index of 2·3 (1·2 to 3·4), and the index for all benzodiazepines combined was 5·7.

Although there are potential sources of error in these studies,[6] a bias that would lead to differences between compounds was not identified.[3] Clinical studies can adjust for potential confounders which studies that use coronial data are unable to take into account. If differences between the benzodiazepines are supported by data from clinical studies this also adds credence to the fatal toxicity index which first noted these findings.

Our aim was therefore to determine if temazepam caused more sedation and oxazepam less sedation than other benzodiazepines when taken in overdose.

Methods

This was a follow up study of consecutive presentations to hospital after self poisoning with benzodiazepines between January 1991 and January 1994. The department has a regional responsibility for all poisonings in the lower Hunter Valley (population about 350 000). The data, collected prospectively by casualty doctors and subsequently verified by the clinical toxicology team, included patient's characteristics (age, sex), all drugs and dose ingested, coingested substances, regular medication, history of abuse of drugs or alcohol, or both, details of management, and complications of poisoning. The state of intoxication was determined by three different but overlapping methods. These were identical with those described by McCarron *et al* for assessing the severity of barbiturate intoxication.[7] A 7 point scale of conscious state (alert, drowsy, stuporous, coma 1-4) was used. Deeper levels of coma indicate loss of response to painful stimuli, inadequate respiration, and hypotension. The Glasgow coma score and McCarron score (a modified Glasgow coma score which includes scores based on vital signs)[7] were also calculated.

STATISTICAL ANALYSIS

Because of the large additive effect on sedation, patients who ingested more than one sedative drug were excluded from further analysis. The outcomes analysed were whether patients were stuporose or comatose on presentation and the mean Glasgow coma and McCarron scores. The differences in potency between benzodiazepines were adjusted for by converting the amount (mg) ingested to defined daily doses.[8] To investigate the strength of the associations between temazepam and oxazepam and the main clinical outcomes we calculated the odds of outcome in those exposed and those not exposed. Odds ratios were adjusted for age, sex, coingestion of alcohol, chronic benzodiazepine use, and dose ingested by logistic regression by using maximum likelihood or an exact method.[9]

Results

During 1991-3, 542 patients with benzodiazepine poisoning presented to this hospital, 239 of these patients, however, had ingested either more than one benzodiazepine or coingested other sedating drugs. The drugs ingested by the remainder were temazepam (64), oxazepam (45), diazepam (113), clonazepam (24), flunitrazepam (21), nitrazepam (18), others (18). Table I compares the characteristics of patients ingesting these drugs.

TABLE I—*Comparison of characteristics of patients ingesting different benzodiazepines*

Characteristic	Oxazepam (n=45)*	Others (n=194)*	Temazepam (n=64)*	P value
No (%) of women	27 (60%)	102 (52%)	45 (71%)	0·03†
Median (range) age (years)	36 (14-82)	31 (14-82)	36 (19-83)	0·02‡
Median (range) time to presentation (minutes)	120 (15-1050)	140 (15-1260)	130 (30-1190)	0·74‡
Median (range) amount ingested (defined daily doses)	10·8 (0·6-39)	12 (0·3-62·5)	10·5 (0·5-30)	0·11‡
No (%) with coingestion of alcohol	21 (47)	71 (36)	22 (35)	0·39†
No (%) with regular use of benzodiazepines	19 (42)	75 (38)	34 (54)	0·10†
No (%) with drug or alcohol abuse	28 (62)	125 (64)	38 (60)	0·86†

*No varies for some variables because of missing data. †χ^2 with 2df. ‡Kruskal-Wallis test.

TABLE II—*Details of coma scores and odds ratios (95% confidence intervals) for sedation for oxazepam and temazepam (compared with all other benzodiazepines)*

Detail	Oxazepam (n=45)	Others (n=194)	Temazepam (n=64)	P value for effect of drug on outcome (test)
Range of Glasgow coma scores	9-15	3-15	4-15	
No (%) with Glasgow coma score <15	6 (14%)	60 (32)	25 (41)	0·01 (χ^2 with 2df)
Median (range) McCarron score	28 (20-30)	28 (12-31)	27 (14-31)	0·27 (Kruskal-Wallis)
No (%) of stuporous or comatose subjects:	2 (4)	38 (19)	16 (25)	0·02 (χ^2 with 2df)
Unadjusted odds ratios	0·19 (0·02 to 0·80†)	1·0	1·41 (0·67 to 2·86†)	
Adjusted odds ratio†	0·21 (0·05 to 0·93)	1·0	1·32 (0·59 to 2·95)	0·02 (Likelihood ratio statistic)
No (%) of comatose subjects:	0	16 (8)	9 (14)	0·03 (χ^2 with 2df)
Unadjusted odds ratio	0·0 (0·0 to 0·85†)	1·0	1·86 (0·68 to 4·77‡)	
Adjusted odds ratio§	0·22 (0·0 to 1·43)	1·0	1·94 (0·57 to 6·23)	0·04 (Scores test)

*No varies for some variables because of missing data.
†Exact 95% confidence interval.
‡Adjusted for age, sex, dose, coingestion of alcohol, chronic use of benzodiazepines, and history of abuse of drugs or alcohol.
§Adjusted for age, sex, dose, and coingestion of alcohol. Exact odds ratio and 95% confidence interval.

Oxazepam was less and temazepam was more sedating than other benzodiazepines with significance obtained for oxazepam in both the unadjusted and adjusted analyses (table II). (In the analysis of coma the odds ratios were adjusted for fewer variables as the others were not needed.)

Discussion

Our results show that there are differences between temazepam, oxazepam, and other benzodiazepines in the degree of sedation they cause in overdose, and the observed differences are not due to confounding by age, sex, dose ingested, coingestion of alcohol, chronic benzodiazepine use, or history of drug or alcohol abuse. This provides a plausible explanation why temazepam and oxazepam have different fatal toxicity indices from other benzodiazepines.[3]

The sedation produced by benzodiazepines in therapeutic doses and overdose has a poor correlation with measured drug concentration but is increased with rapid absorption.[1 10-12] Temazepam is more rapidly absorbed and oxazepam is more slowly absorbed than most other benzodiazepines.[1 10-13] Further research is required to determine if the rate of absorption is different in overdose and is sufficient to explain the differences in sedation. Slowing the rate of absorption may reduce toxicity, but this would also reduce their sedative effect in therapeutic doses.[11] Drug regulatory authorities should be aware that changes in formulation of benzodiazepines may affect toxicity in overdose.

Pharmacodynamic factors such as benzodiazepine receptor affinity and potency may also be important. Because of the wide variations in half life, adjustments for dose by conversion into defined daily doses or diazepam equivalents[14] is imperfect. These are designed to compare use rather than potency. Though they correlate reasonably well with sizes of prescriptions and tablets, they may not account for potency per tablet taken in overdose. Differences in potency could also explain the results in both our study and that of Serfaty and Masterton.[3]

Flurazepam, now rarely prescribed in the United Kingdom and Australia, had the highest fatal toxicity index of any benzodiazepine (15·0).[3] It has also been found to be more sedating in overdose than diazepam and chlordiazepoxide.[10] That study and our own support the differences between drugs noted in the fatal toxicity index.[3] If the coroners' data on which this index is based are reliable enough to detect small differences in toxicity between drugs then it gives credence to other work based on these data, according to which, temazepam is the sixth most common cause of death attributable to a single drug in the United Kingdom.[15] in contrast, there have been only a few deaths directly attributed to benzodiazepine poisoning reported in the medical literature.[1 16 17] Benzodiazepines are the most common prescription drugs taken in overdose.[18] Although all these drugs are much safer than barbiturates and sedating tricyclic antidepressants,[3-5] they should not be prescribed to patients at high risk of suicide. Differences between benzodiazepines may be relevant when prescriptions are dispensed for depressed or suicidal patients, and appropriate choices may lead to a considerable reduction in lives lost to suicide.

Key messages

- Benzodiazepines are commonly taken in overdose and have generally been assumed to be safe
- In a recent study of coronial data large differences were noted in the number of fatal poisonings caused by different benzodiazepines (after correction for market share)
- This study provides evidence that there are differences, both before and after adjustment for a number of potential confounders, between benzodiazepines in the incidence with which they cause major sedation in overdose
- These clinical differences provide explanation and support for the coronial data
- Benzodiazepines cannot be assumed to be safe in patients at risk of self poisoning, but some benzodiazepines seem to be safer than others

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Relative mortality from overdose of antidepressants

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See pp 215, 219, and editorial by Edwards

Abstract

***Objective*—To compare the fatal toxicities of antidepressant drugs in 1987-92.**

***Design*—Retrospective epidemiological review of prescription data of the Department of Health, Scottish Office Home and Health Department, and Welsh Health Common Services Authority (excluding data from most private general practices and most hospitals), and mortality data from the Office of Population Censuses and Surveys and General Register Office in Scotland.**

***Setting*—General practice, England, Scotland, and Wales.**

***Main outcome measures*—Deaths per million prescriptions and deaths per defined daily dose.**

***Results*—81·6% (1310/1606) of deaths from antidepressant overdose were due to two drugs, amitriptyline and dothiepin. The overall average of deaths per million prescriptions was 30·1. The overall rate for tricyclic drugs was 34·14 (95% confidence interval 32·47 to 38·86; $P<0·001$), monoamine oxidase inhibitors 13·48 (6·93 to 22·19; $P<0·001$), atypical drugs 6·19 (4·04 to 8·80; $P<0·001$), and selective serotonin reuptake inhibitors 2·02 (0·64 to 4·17; $P<0·001$). The numbers of deaths per million prescriptions of amoxapine, dothiepin, and amitriptyline were significantly higher than expected, while nine drugs had a significantly lower number of deaths per million prescriptions than expected. Analysis of deaths per defined daily dose showed a similar pattern.**

***Conclusions*—Safety in overdose should be considered in risk-benefit and cost-benefit considerations of antidepressants. A switch in prescribing, from drugs with a high number of deaths per million prescriptions to drugs with a low number, could reduce the numbers of deaths from overdose. Although this form of suicide prevention can be implemented easily and immediately, its introduction needs to be considered against the higher costs of some of the newer drugs.**

Introduction

While little demonstrable difference exists between antidepressants in terms of efficacy,[1] toxicity in overdose varies widely.[2] We compared the fatal toxicities of antidepressants currently available in Britain individually and by group during 1987-92, during which time the selective serotonin reuptake inhibitors were introduced.

Methods

Antidepressants were assigned to four classes: monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, and the so called "atypical"[3] antidepressants. We obtained numbers of deaths in England, Wales, and Scotland due to acute poisoning by a single antidepressant.[4,5] The statistics and research division of the Department of Health supplied data on the number of antidepressant prescriptions for general medical practices within the NHS for England, Wales, and Scotland for 1987-9 and for England for 1990-2; for 1990-2 the Scottish data were provided by the Scottish Office Home and Health Department and the Welsh data by the Welsh Health Common Services Authority. Private general practice and most hospitals were excluded; figures for 1991 and 1992 include dispensing practices. About three quarters of all drug prescriptions are written by general practitioners.[6,7] Most patients with psychiatric disorders, however, are treated by general practitioners rather than by psychiatrists[8-10] (90% to 98% of depressed patients[8-11]). The exclusion of hospital prescriptions from our analysis should not, therefore, appreciably affect the outcome of this study.

We calculated the number of deaths per million prescriptions during the six years for all the drugs taken together; for each of the four groups of antidepressants; and for each drug individually. The χ^2 test was applied to the groups of antidepressants. The expected numbers of deaths are given for the individual drugs, with Fisher's exact test (one tailed) applied to the data. Confidence limits are calculated as $x \pm 1·96$ SD(x).

Using the prescribed data, we considered each preparation of each drug analysed, multiplied the strength of the preparation by the quantity prescribed, and divided this by the defined daily dose values (obtained from the World Health Organisation).[12,13] We calculated the number of defined daily doses per prescription for each drug and the number of deaths per million defined daily doses prescribed.

Results

The mean annual number of deaths due to overdose with a single antidepressant over the six years was 268 (range 238 to 288). The tricyclic drugs were implicated in most deaths (table I), with two drugs—amitriptyline and dothiepin—accounting for 81·6% of all deaths. Tables II and III show the figures for mortality and data for prescriptions for deaths per million prescriptions for the four groups of drugs for the six years. The tricyclic antidepressants as a group

TABLE I—*Mean yearly numbers of deaths from tricyclic and other antidepressants, 1987-92*

Cause of death	Death from tricyclic drugs	Death from non-tricyclic drugs
Suicide with single antidepressant	150	4
Suicide with more than one substance, including antidepressants	240	10
Overdose with single antidepressant	260	12
Overdose with more than one substance, including antidepressants	424	24

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