Int J Legal Med (2005) 119: 344–348
DOI 10.1007/s00414-005-0528-x

ORIGINAL ARTICLE

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Newer antidepressants: evaluation of fatal toxicity index and interaction with alcohol based on Finnish postmortem data

Received: 25 October 2004 / Accepted: 19 January 2005 / Published online: 1 March 2005

Abstract Finnish postmortem toxicology data from 1995 to 2002 was analyzed to obtain improved estimates of fatal toxicity indices for the newer antidepressants and to evaluate their interaction with alcohol. Altogether 284 fatal poisonings were attributed to 12 different newer antidepressants. Venlafaxine, mianserin, moclobemide, and mirtazapine were responsible for significantly more deaths than expected from their sales. Their fatal toxicity indices were higher than those of selective serotonin reuptake inhibitors (SSRIs) but lower than those of tricyclic antidepressants. In fatal poisonings involving alcohol in combination with venlafaxine, mianserin, moclobemide, or mirtazapine, the median blood alcohol concentration (BAC) ranged from 2.35 to 2.7 mg/g, whereas in those involving alcohol in combination with citalopram or fluoxetine the median BAC was 2.9 and 3.4 mg/g, respectively. The BAC was significantly lower in venlafaxine-related deaths than in those involving fluoxetine or citalopram. We conclude that among the newer antidepressants differences are present both in toxicity and in interaction potential with alcohol. The SSRIs appear to present a low risk of fatal poisoning when taken alone or in combination with alcohol, whereas venlafaxine is associated with an elevated risk.

Keywords Drugs · Alcohol · Interaction · Forensic · Fatal toxicity index

Introduction

The use of antidepressants in the Western world has increased dramatically during the last two decades. The newer antidepressants, i.e., antidepressants introduced since the early 1980s, have proven to be efficacious and well tolerated [1–3], and they also seem safer in overdose, resulting in a milder clinical course in hospitalized patients and fewer fatal poisonings [4, 5]. Selective serotonin uptake inhibitors (SSRIs), in particular, seldom provoke cardiovascular side-effects [6, 7]. In addition to the SSRIs, the newer antidepressants include several other agents listed in Table 1. Although structurally different, all of these agents are considered to have a mechanism of action based on the monoamine hypothesis, recently discussed in reviews by Delgado [8] and Elhwuegi [9].

In deaths where newer antidepressants are found, other toxic compounds are predominantly present [4, 10]. Low fatal toxicity indices (FTIs) have been reported for the newer antidepressants [5, 11, 12], although for some substances, e.g., mianserin and mirtazapine, the reported FTIs have been based on marginal consumption and only a few fatalities. By contrast, tricyclic antidepressants (TCAs) have high FTIs [5, 11–14] and they remain among the most frequently occurring drugs in fatal poisonings, especially suicides [14–16]. Furthermore, the TCAs amitriptyline and doxepin appear to interact with alcohol in a fatal manner [15], whereas most of the newer antidepressants have not yet been evaluated in this respect.

Therefore, with the intention of offering new insight into the interpretation of forensic toxicology results, our objective was to establish more precise FTIs for the newer antidepressants and to investigate their possible interaction with alcohol using postmortem material.

Materials and methods

Drug consumption in 1995–2002 was obtained from the Finnish National Agency of Medicine and expressed as defined daily doses (DDD) per 1000 inhabitants per year (DDD/1000 inh./year), with DDDs as defined by the Nordic Council of Medicines (Table 1). Mirtazapine and venlafaxine were introduced in 1997, nefazodone and reboxetine in 1998, and milnacipran in 2001. Due to a combined market share of less than 1% of all antidepressants, milnacipran, nefazodone, trazodone, and reboxetine were excluded from FTI calculations. The TCAs amitriptyline and doxepin were included for comparison.

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Table 1 Newer antidepressants in Finland in 1995–2002

Drug	DDD (mg)	Sales[a]	Deaths		*p* value[b]	Fatal toxicity index (95% CI)[c]	
			Observed	Expected			
Citalopram (SSRI)	20	84.0	104	114		1.2	(1.0–1.5)
Fluoxetine (SSRI)	20	48.9	16	66	<0.001	0.33	(0.19–0.53)
Sertraline (SSRI)	50	15.7	6	21	0.003	0.38	(0.14–0.83)
Mirtazapine	30	14.5	37	20	0.017	2.6	(1.8–3.5)
Paroxetine (SSRI)	20	11.2	16	15		1.4	(0.82–2.3)
Mianserin	60	10.9	33	15	0.006	3.0	(2.1–4.3)
Moclobemide	300	10.9	29	15	0.027	2.7	(1.8–3.8)
Venlafaxine	100	6.80	30	9	<0.001	4.4	(3.0–6.3)
Fluvoxamine (SSRI)	100	5.26	8	7		1.5	(0.66–3.0)
Others[d]		1.12	5	2			
Total		209.1	284			1.4	(1.2–1.5)

SSRI selective serotonin reuptake inhibitor, *DDD* defined daily dose
[a]In DDD/1000 inhabitants/year (Finnish National Agency of Medicine)
[b]*p* value for the difference between the proportions of observed and expected deaths
[c]95% confidence interval calculated from observed deaths using the Poisson distribution
[d]Includes trazodone, nefazodone, milnacipran, and reboxetine

The number of fatal antidepressant poisonings was obtained from the laboratory database, into which the most important finding, cause of death, and manner of death assigned by the pathologist had been recorded from a copy of a completed death certificate. For amitriptyline and doxepin, published figures were used for 1995–2001 [17–20].

Drug and alcohol concentrations were measured in femoral venous blood collected into plastic tubes (1% NaF) at medico-legal autopsies performed in Finland during 1995–2003. At the Forensic Toxicology Division, University of Helsinki, the samples were submitted to a quantitative blood alcohol screen, a broad drug screen, and, when required, further analyses. The blood alcohol concentrations (BACs) were obtained using head-space gas chromatography [21] and reported to two significant digits in mass per mass units as parts per thousand (‰). The lower limit of quantitation for ethanol was 0.20‰. The antidepressant concentrations were determined using gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry.

The data for the BAC-related statistical analyses included (1) cases of fatal alcohol (ethanol) poisoning in which citalopram, fluoxetine, mianserin, mirtazapine, moclobemide, or venlafaxine was found in femoral blood in concentrations in or above the therapeutic range; (2) fatal poisonings by any of these six drugs with alcohol detected in blood. Cases with other toxicologically significant findings were excluded, excepting those with therapeutic concentrations of benzodiazepines (BDZs), commonly prescribed to depressed patients for comorbid anxiety and insomnia.

Statistical analysis

MINITAB 13.31 was used for statistical analysis. The expected number of deaths was derived from the market share and compared with the observed number of deaths using the test for two proportions. For FTIs, 95% confidence intervals (CIs) were calculated using the Poisson distribution, and differences were considered significant when the CIs did not overlap. The Mann–Whitney test was applied to the differences between median BACs.

Results and discussion

Sales

The consumption of newer antidepressants has increased heavily in Finland in 1995–2002, with citalopram and fluoxetine nowadays the most common antidepressants (Table 1). The most common TCAs have, however, remained in use: in 2002, consumption of amitriptyline was 3.81 DDD/1000 inh./year and consumption of doxepin 1.15 DDD/1000 inh./year.

Deaths

A newer antidepressant was the most important finding in 284 fatal poisonings (Table 1). Of these poisonings, trazodone caused three, nefazodone one, milnacipran one, and reboxetine none. Amitriptyline was denoted as the most important finding in 348 and doxepin in 257 fatal poisonings. Among the common newer antidepressants, fluoxetine and sertraline had caused significantly less and the non-SSRI agents significantly more deaths than expected.

Fatal toxicity index

The fatal toxicity indices (FTIs) (expressed in deaths/DDD/1000 inh./year) calculated for the newer antidepressants ranged from 0.33 (fluoxetine) to 4.4 (venlafaxine), with an overall average of 1.4 (Table 1), whereas the FTIs of amitriptyline and doxepin were 12 (95% CI 10–13) and 22 (95% CI 19–25), respectively. Fluoxetine and sertraline had significantly lower and mirtazapine, moclobemide, mianserin, and venlafaxine significantly higher FTIs than the overall average. In addition to fluoxetine and sertraline, citalopram had a lower FTI than the non-SSRI agents. In general, all of the SSRIs had significantly lower FTIs than venlafaxine. A similar observation was reported earlier by Buckley and McManus [12] on the basis of British prescription and mortality data for 1993–1999. The FTI for venlafaxine was,

Table 2 Characteristics of 150 fatal poisonings involving newer antidepressants and alcohol

	Number	Gender	Age (years)	Manner of death		BAC	
				Accident	Suicide		
		Male (%)	Mean (range)	*n* (%)	*n* (%)	Median	95% CI
Citalopram	80	52 (65)	46 (22–76)	66 (83)	9 (11)	2.9	2.5–3.2
Fluoxetine	21	13 (62)	47 (27–69)	18 (86)	2 (10)	3.4	3.0–3.9
Mianserin	16	12 (75)	48 (32–68)	7 (44)	7 (44)	2.35	1.7–2.9
Mirtazapine	16	11 (69)	45 (36–61)	11 (69)	4 (25)	2.7	2.3–3.2
Moclobemide	9	8 (89)	43 (20–58)	5 (56)	3 (33)	2.7	1.1–3.9
Venlafaxine	8	3 (63)	53 (29–81)	5 (63)	2 (25)	2.35	0.4–2.7
Total	150	99 (66)	47 (20–81)	112 (75)	27 (18)	2.9	2.6–3.1

BAC blood alcohol concentration

however, in both studies significantly lower than that of the TCAs amitriptyline and doxepin.

In 1995 antidepressants caused 8.4% of all suicides committed in Finland, with 82% of antidepressant suicides attributed to amitriptyline and doxepin [14]. The FTIs of these drugs were high, 12.1 and 21.3, respectively, whereas the newer antidepressants moclobemide (4.8), mianserin (3.2), citalopram (1.8), and fluoxetine (1.1) had significantly lower FTIs. The current results largely parallel these values. On mirtazapine and venlafaxine, however, the FTIs presented here yield novel information since these drugs were introduced in Finland after the study period covered by Öhberg et al. [14] and since mirtazapine was represented by a single fatality in the study of Buckley and McManus [12].

Drug–alcohol poisonings

Six of the newer antidepressants were involved in a sufficient number of fatal drug–alcohol poisonings to allow statistical evaluation of blood drug and alcohol concentrations. Main characteristics of the 150 poisonings are shown in Table 2. The manner of death was in all cases accidental, suicide, or undetermined. No significant differences in age or gender were present between the drugs. When alcohol was the most important finding, 96% of cases were accidental, with no suicides. Of the cases with an antidepressant denoted as the most important finding, 46% were suicides and 42% accidental. Normal or therapeutic concentrations of BDZs were present in 65% of cases, which is more than the 40% average of all BDZ findings for postmortem cases in drug screening [22].

The median BAC for these 150 cases was 2.9‰ (Table 2). The median BAC was significantly lower in fatal poisonings involving venlafaxine (2.35‰, p=0.005) and mianserin (2.35‰, p=0.009) than in those involving fluoxetine (3.4‰). In venlafaxine cases, the highest BAC was only 3.0‰ and the median BAC was also significantly lower than in cases involving citalopram (2.9‰, p=0.035). The median BAC in accidental deaths was significantly higher than the median in suicides (3.1‰ vs 2.0‰, p<0.001), but similar to the median observed in a series of accidental alcohol poisonings caused by ethanol alone (3.3‰) [23].

Cases involving citalopram, the most common antidepressant in our drug–alcohol data (53%), were analyzed further. In these 80 cases, average citalopram concentrations (median 0.6 mg/l, mean 1.6 mg/l) were similar to those found in as series of 20 Danish autopsy cases where citalopram together with other substances was considered the cause of death (median 0.8 mg/kg, mean 1.2 mg/kg) [24]. Alcohol

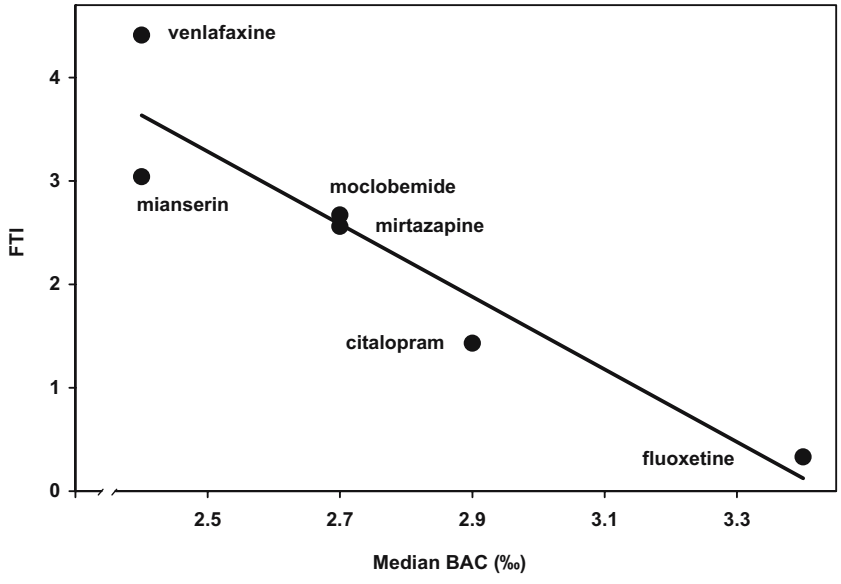

Fig. 1 Fatal toxicity index (*FTI*) of certain new antidepressants and median blood alcohol concentrations (*BAC*) found in fatal poisonings involving alcohol and an antidepressant

had been denoted as the most important finding in 55 cases, citalopram in 25. Of the 12 poisonings where citalopram concentration exceeded 1.5 mg/l, only one fatality had been primarily attributed to alcohol. Conversely, of the 44 poisonings where BAC exceeded 2.8‰, only one fatality had been primarily attributed to citalopram.

Drug safety

Based on the FTI and BAC data presented above, the SSRIs appear relatively safe, whereas venlafaxine, mianserin, moclobemide, and mirtazapine can be considered the least safe among the common newer antidepressants (Fig. 1). For mianserin, mirtazapine, and moclobemide, this is a novel result considering the wide CIs for the FTIs presented previously [12]. In contrast, the relatively high toxicity of venlafaxine and the relative safety of SSRIs have already been established by a number of studies [6, 12, 16, 25], with the underlying rationale offered from many perspectives, most recently in a comprehensive discussion by Cheeta et al. [10].

Explanations for the high venlafaxine-related mortality include the following. Venlafaxine may inherently be relatively toxic. Furthermore, if venlafaxine is presumed to be more toxic than SSRIs, it is also more likely to be denoted as the primary cause of death. Prescribing practices may also be different for venlafaxine than for SSRIs, with venlafaxine prescribed to people already at a relatively high suicide risk [26, 27]. This hypothesis is supported by the finding that psychotropic agents are often present in venlafaxine-related deaths [10]. In addition to venlafaxine, the above rationale might apply to mirtazapine, another dual-action antidepressant [28]. In a recent report relating hospital admissions to prescription data, the rates of overdose-associated admissions were significantly higher for venlafaxine and mirtazapine than for antidepressants in general [29].

The low mortality associated with SSRIs may in part arise from their being prescribed for other conditions besides depression, conditions which are often associated with a lower risk of suicide. Moreover, the SSRIs are generally tolerable at effective doses, resulting in good compliance and eventual improvement of the condition. It is, however, difficult to evaluate their role in drug-related deaths, since in overdose situations they are predominantly found in combination with alcohol, BDZs, or other antidepressants [4, 10]. The possibility of drug interactions, such as increased risk of serotonin toxicity and inhibition of certain metabolic enzymes, further complicates the interpretation of forensic toxicology results.

In a recent study on deliberate self-poisonings, use of an antidepressant was found to be associated with a relatively mild clinical course. This unanticipated finding was attributed to the increased proportion of newer, less toxic antidepressants [30]. All in all, our results confirm that the newer antidepressants are much safer than other common drugs involved in fatal intoxications, and the differences in toxicity between the newer antidepressants are small.

Conclusions

The newer antidepressants are increasingly common findings in postmortem investigations, presenting new challenges for the interpretation of forensic toxicology results. This study demonstrates that among the newer antidepressants, venlafaxine, mianserin, moclobemide, and mirtazapine cause significantly more deaths than expected from their sales. They thus have higher FTIs than the SSRIs. Moreover, in fatal poisonings involving these agents, the median BACs were lower than in those involving citalopram or fluoxetine, indicating an additive or synergistic interaction with alcohol. We therefore conclude that the SSRIs appear to pose a lower risk of fatal poisoning both when taken alone and in combination with alcohol.

Acknowledgements This study was supported by a grant from the Finnish Foundation for Alcohol Studies.

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