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ARTICLE

Lack of significant toxicity after mirtazapine overdose: A five-year review of cases admitted to a regional toxicology unit

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Introduction. Mirtazapine is a comparatively new antidepressant that selectively blocks central α2-adrenergic autoreceptors and postsynaptic 5-HT_2 and 5-HT_3 receptors, causing reduced neuronal norepinephrine and serotonin reuptake. The prevalence of mirtazapine prescribing has steadily risen; however, comparatively little information is available regarding the clinical features associated with mirtazapine overdose. *Aims.* To characterize the toxic features that result from mirtazapine overdose. *Methods.* We performed a retrospective case analysis of patients admitted to the Toxicology Unit of the Royal Infirmary of Edinburgh between January 2000 and December 2004 after stated mirtazapine overdose. Casenotes were examined for clinical, laboratory, and electrocardiographic safety data. *Results.* There were 117 mirtazapine cases where the median (interquartile range) stated dose ingested was 450 mg (240–785 mg). Conscious level was reduced in 27.2% of patients and there was a higher incidence of tachycardia (30.4%) than predicted from normal reference range values ($p < 0.001$). There was no evidence of any other significant clinical, laboratory, or electrocardiographic abnormality. *Conclusions.* Severe toxic features could be attributed to other co-ingested drugs or alcohol. The adverse clinical effects attributable to mirtazapine overdose appeared mild and predictable. Mirtazapine overdose appears to be associated with fewer features of severe toxicity than previously reported for other antidepressants.

Keywords Electrocardiograph, Safety monitoring, Drug toxicity

Introduction

Mirtazapine (Zispin®, Remeron®) was developed by Organon, and first became available for clinical use in 2001. It is a 6-aza analogue of the tetracyclic antidepressant mianserin (1). Unlike other antidepressants that inhibit neurotransmitter uptake, the pharmacological effects of mirtazapine in the central nervous system are thought to be due to the blockade of presynaptic α2-adrenergic receptors and postsynaptic 5-HT_2 and 5-HT_3 receptors, which results in an increased noradrenergic and 5-HT_{1A}-mediated serotonergic activity (2,3). Mirtazapine also has a high affinity for central $histamine_1$ receptors (4). Clinical trials show mirtazapine to be at least as efficacious as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) in the treatment of major depression (5,6). Furthermore, mirtazapine appears to have an earlier onset of action than other antidepressants; possibly as a result of its unique mechanism of action (7). It is available in a variety of formulations, including a rapidly soluble oral formulation (SolTab®) and an intravenous preparation (8). The usual daily treatment dose is 15 to 45 mg, which is normally given at bedtime or occasionally in divided doses.

The use of mirtazapine has progressively increased after it became available, and prescription monitoring suggests that it is free of any major adverse clinical effects across large patient populations (9). A number of other adverse effects include drowsiness, increased appetite and weight gain, dizziness and headache, postural hypotension, tremor, and arthralgia (9). Relatively little information is available regarding the clinical features associated with mirtazapine overdose. Therefore, we wished to examine the clinical features after a mirtazapine overdose among patients admitted to the Toxicology Unit of the Royal Infirmary of Edinburgh, and to examine laboratory and electrocardiographic safety variables so as to better characterize the toxicity profile of mirtazapine.

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Methods

We performed a retrospective review of casenotes from patients admitted to our unit between January 2000 and December 2004, inclusive, after taking a mirtazapine

overdose. Cases were identified from a local register of patients attending the Royal Infirmary of Edinburgh. While community toxicological advice is available to medical professionals in the United Kingdom via the National Poisons Information Service, this is unlikely to have reduced the number of patients attending the hospital because little was known about the potential toxic effects of mirtazapine at the time of the study. Our local policy is that patients attending the Emergency Department after drug ingestion are admitted to our Toxicology Unit for ongoing medical care and psychiatric review. Patients will be admitted to the High Dependency Unit (HDU) if non-invasive ventilatory support is likely to be required, and to the Intensive Treatment Unit (ITU) if invasive ventilatory support, haemodialysis or other critical care intervention is likely to be required. Patients in all of these areas were included in the study.

Data collection

A standardized data collection sheet was used, and data were linked to a unique hospital code so as to preserve patient anonymity. The date and time of overdose, stated amount ingested, type and amount of any co-ingested drug or alcohol, time elapsed between ingestion and hospital attendance, age and gender, and any history of previous overdose, drug or alcohol dependence were recorded. Clinical data recorded were symptoms reported on arrival at the hospital, Glasgow Coma Scale, heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation. Laboratory data examined were serum urea, creatinine, electrolytes, creatinine kinase, and liver biochemistry. Automated electrocardiographic intervals PR, QRSD, QT and QTc were recorded, where QTc represented the QT interval after Bazett's correction (10).

Where more than one clinical, laboratory or electrocardiographic variable had been documented, the most abnormal value was used in safety data analysis.

Prescribing data

Data on community prescribing of mirtazapine was obtained from the Lothian Health Board, which pertains to the same patient population as served by our hospital. The data are expressed as General Practitioner prescriptions items for mirtazapine per quarter for the whole population of Lothian (estimated 784,000).

Statistical analyses

Normality tests found that data were not distributed parametrically and, therefore, median and interquartile ranges were used as descriptive statistics with population ranges quoted where appropriate. Abnormal variables were identified as those outside the normal 95% population reference values, and statistical significance determined by binomial tests. StatsDirect™ statistical software version 2.2.2 (StatsDirect Ltd., Cheshire, UK) was used to perform post-hoc binomial power calculations, and to examine correlations between stated mirtazapine dose and safety variables. Pearson's r-values were subjected to Fisher's transformation to give for 95% confidence intervals, and $p < 0.05$ was accepted as statistically significant in all cases.

Results

Between 2000 and 2004, 153 admission records contained mention of mirtazapine or Zispin®. Medical casenotes were available for all of these, but 36 were excluded because patients had not reported taking a mirtazapine overdose, and the remaining 117 cases were included in the formal data analyses. The frequency of patients admitted to our unit after ingesting mirtazapine has risen over the study period, and is consistent with increasing numbers of mirtazapine prescriptions issued in our region (Fig. 1).

Median (interquartile range) [population range] age was 35 y (26–46 y) [18–80 y], and 71 (60.7%) ingestions occurred in women. The median stated amount of mirtazapine ingested was 450 mg (240–785 mg) [30–2520 mg], and patients had presented to the hospital 1.6 h (1.1–3.2 h) [0.5–48.0 h] after ingestion. Deliberate self-inflicted trauma (e.g., self-cutting) was evident in three patients (2.6%) at the time of presentation to hospital.

Co-ingested drugs and alcohol

Mirtazapine overdose was associated with co-ingestion of alcohol in 69 patients (59.0%), other drugs in 70 patients (59.8%), both alcohol and other drugs in 45 patients (38.5%), and neither in 23 patients (19.7%). Mirtazapine overdose was associated with co-ingestion of one other drug in 36.8%, two other drugs in 11.1%, and three or more other drugs in 12.0%.

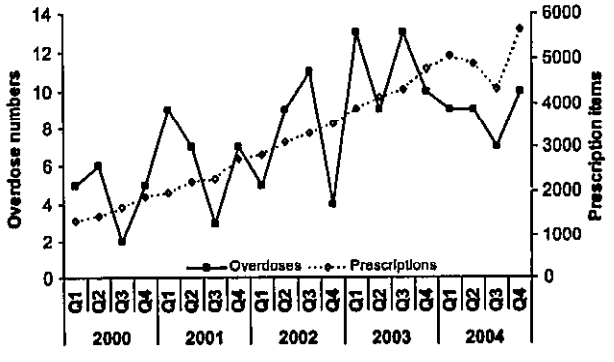

Fig. 1. Quarterly numbers of patients admitted to the hospital after mirtazapine overdose during 2000–2004, and corresponding numbers of prescriptions issued locally.

The most commonly co-ingested medications were benzodiazepines (20.6%), other antidepressants (15.0%), antipsychotics (10.8%), acetaminophen (7.8%), opiates (6.9%), and co-codamol (acetaminophen-codeine combination, 3.9%). To better characterize the potential effects of mirtazapine in overdose, data were examined across three groups: (1) the whole population, (2) the subgroup of patients who had not co-ingested other drugs, and (3) the further subgroup who had not co-ingested other drugs or alcohol.

Clinical safety data

On arrival to the hospital, 27.2% of patients reported drowsiness or fatigue, and the remainder were asymptomatic. Six patients had reduced Glasgow Coma Scale (GCS) <14 (5.1%). In these six, the stated amount of ingested mirtazapine was 720 mg (450–1020 mg), and five patients had co-ingested alcohol. In one patient, GCS was 3 on arrival to hospital, 1.5 h after taking mirtazapine 210 mg with large quantities of chlorpromazine and alcohol; this patient was monitored in a High Dependency Unit but recovered quickly and no specific treatment was needed. Another patient presented with GCS 6, 3 h after taking unknown quantities of mirtazapine, carbamazepine, promethazine and diazepam, and required temporary invasive ventilation in the Intensive Care Unit.

Vital signs were documented in the casenotes in 115 patients (98.2%), and the occurrence of abnormal values is summarized in Table 1. Heart rate was 87 min^{-1} (76–103 min^{-1}), and systolic and diastolic blood pressures were 125 mmHg (114–140 mmHg) and 71 mmHg (63–80 mmHg), respectively. Respiratory rate was 16 min^{-1} (14–18 min^{-1}), oxygen saturation was 97% (95–98%), and body temperature was 36.5°C (36.2–37.0°C).

Laboratory and electrocardiographic safety data

The prevalence of abnormal values is presented in Table 1, and correlations between stated mirtazapine dose and safety variables are presented in Table 2. Laboratory data were available for 103 patients (88.0%). No major electrolyte disturbance was documented in any patient. Mild hypernatraemia (7.8%, $p = 0.004$) and mild hypokalaemia (15.5%, $p < 0.001$) were found in patients who had co-ingested other drugs or alcohol, and high ALT (7.8%, $p = 0.004$) and GGT (12.6%, $p < 0.001$) were found in patients who had co-ingested other drugs. There was no significant correlation between stated mirtazapine dose and serum sodium or potassium concentrations.

An electrocardiograph was available for 103 patients (88.0%). Median PR interval 151 ms (140–162 ms), QRS 86 ms (79–92 ms), QT 342 ms (322–368 ms), and QTc 416 ms

Table 1. Summary of abnormal clinical, laboratory and electrocardiograph findings are shown as absolute number and percentage in parentheses

	Study population (n = 117)	No co-ingested drugs (n = 47)	No co-ingested drugs or alcohol (n = 23)
Previous OD	82 (70.1)	31 (66.0)	17 (73.9)
Haemodynamics	**n = 115**	**n = 46**	**n = 23**
HR >99	35 (30.4)***	13 (28.3)***	5 (21.7)***
HR <61	6 (5.2)	3 (6.5)	3 (13.0)*
SBP <100	6 (5.2)	1 (2.2)	0 (0.0)
SBP >160	5 (4.3)	3 (6.5)	2 (8.7)
DBP <50	3 (2.6)	0 (0.0)	0 (0.0)
DBP >90	8 (7.0)*	3 (6.5)	2 (8.7)
RR <8	0 (0.0)	0 (0.0)	0 (0.0)
RR >18	15 (12.8)***	3 (6.5)	2 (8.7)
O2 <92%	1 (0.9)	0 (0.0)	0 (0.0)
Laboratory tests	**n = 103**	**n = 39**	**n = 20**
Na <135	2 (1.9)	0 (0.0)	0 (0.0)
Na >145	8 (7.8)**	4 (10.3)*	0 (0.0)
K <3.5	16 (15.5)***	5 (12.8)**	1 (5.0)
K >5.1	0 (0.0)	0 (0.0)	0 (0.0)
Creat >120	2 (1.9)	1 (2.6)	1 (5.0)
ALT > 50	8 (7.8)**	1 (2.6)	0 (0.0)
GGT >79	13 (12.6)***	2 (5.1)	1 (5.0)
CK >400	4 (3.9)	2 (5.1)	0 (0.0)
ECG data	**n = 103**	**n = 39**	**n = 22**
PR >200 ms	2 (1.9)	1 (2.6)	1 (4.5)
QRSD >120 ms	1 (1.0)	0 (0.0)	0 (0.0)
QTc >450 ms	4 (3.9)	1 (2.6)	0 (0.0)

*p<0.05, **p<0.005, ***p<0.001 by binomial testing, assuming a 0.025% population chance.

Table 2. Correlation between stated amount of mirtazapine ingested and safety variables

Covariate	r value	Fisher's z transform 95% CI	Two-sided p-value
Haemodynamics	**n = 115**		
HR	0.074	−0.130 to 0.271	0.477
SBP	0.006	−0.192 to 0.203	0.953
DBP	0.037	−0.162 to 0.233	0.717
RR	0.011	−0.213 to 0.235	0.922
Laboratory tests	**n = 103**		
Na	−0.090	−0.298 to 0.127	0.418
K	−0.065	−0.275 to 0.152	0.558
Urea	0.164	−0.049 to 0.362	0.13
Creatinine*	0.267	0.059 to 0.452	0.013
ALT	−0.092	−0.314 to 0.139	0.436
GGT	0.008	−0.223 to 0.237	0.949
CK	0.165	−0.091 to 0.400	0.204
ECG data	**n = 103**		
PR	−0.099	−0.301 to 0.112	0.357
QRSD	0.042	−0.168 to 0.248	0.694
QTc (men)	0.073	−0.257 to 0.388	0.666
QTc (women)	0.152	−0.126 to 0.108	0.281

*$p < 0.05$.

(401–429 ms). A 30-year-old man had a short-lived episode of supraventricular tachycardia 19 hours after claiming to have taken mirtazapine 600 mg, acetaminophen 10 g and 2 pints of lager, which was asymptomatic and terminated spontaneously (Fig. 2).

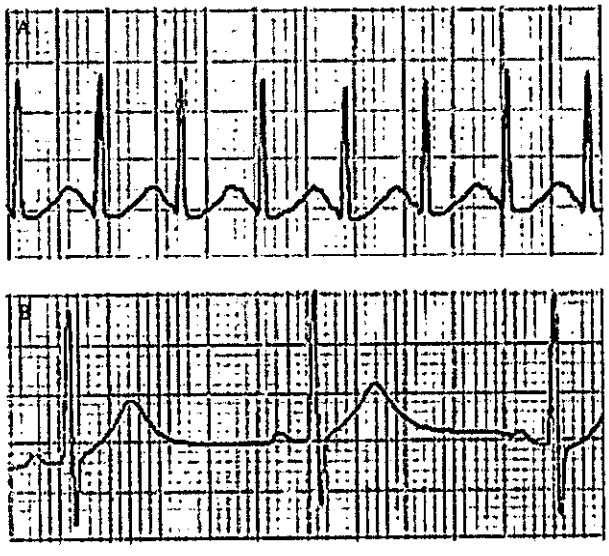

Fig. 2. Short-lived episode of supraventricular tachycardia (A) in a 30-year-old man who alleged to have ingested mirtazapine 600 mg, acetaminophen 10 g and 2 pints of lager 19 hours earlier, which reverted spontaneously to sinus rhythm (B). Electrocardiogram gridlines represent 1 mm divisions, calibrated at 25 mm/s and 10 mm/mV.

Clinical course and outcome

Gut decontamination methods were not routinely administered after mirtazapine ingestion. Two patients were admitted to a critical care facility, and the remaining patients were managed solely in a general medical ward. Twelve patients (10.3%) required specific treatment; 11 of these received N-acetylcysteine for concomitant acetaminophen ingestion. One patient with fever and high serum creatinine kinase received a single dose of cyproheptadine for suspected serotonergic syndrome; however, he was subsequently diagnosed with pneumonia and received oral antibiotics. One patient had a lower urinary tract infection and was treated with antibiotics and intravenous fluids.

The duration of stay in the hospital was 1 day [0–8 days]; 104 patients (88.9%) were discharged home and 13 (11.1%) transferred to a psychiatric facility for further assessment and treatment. Thirteen patients (11.1%) required more than one overnight stay in hospital, including two who had taken mirtazapine alone: one of these required treatment for a urinary tract infection, and the other needed to wait for an available bed in a psychiatric hospital.

Discussion

To the best of our knowledge, these findings represent the largest series of mirtazapine overdose patients reported thus far. A significant number of patients in this study had co-ingested alcohol and other drugs, as would be anticipated in such a patient group. A wide range of doses of mirtazapine were claimed to have been ingested, up to an acute ingestion of 2520 mg.

The major complication observed after mirtazapine ingestion was drowsiness and reduced conscious level in almost 28% of patients, but this did not necessitate any specific intervention in patients who had ingested mirtazapine alone. This is likely due to antagonism of central histamine$_1$ receptors, for which mirtazapine has a high affinity (4). In therapeutic doses, sedation is mild and thought to be offset by increased noradrenergic activity (11). In the present study, ventilatory support was required for one patient who had co-ingested large amounts of other sedative drugs, whereas mirtazapine itself did not appear to cause significant respiratory depression in the overall study group, even after large quantities were stated to have been taken.

Tachycardia was common after mirtazapine ingestion, and the heart rate observed in our patients (median 87 min^{-1}, range 54–140 min^{-1}) was consistent with a comparable patient group after ingestion of SSRI antidepressants (median 87 min^{-1}, range 54–171 min^{-1}), but less than after ingestion of tricyclic antidepressants (96 min^{-1}, 60–180 min^{-1}) or venlafaxine (100 min^{-1}, 56–138 min^{-1}) (12). Tachycardia is unlikely to have been caused by baroreceptor reflex activation because significant hypotension was not observed. Mirtazapine might have increased heart rate as a direct or indirect

drug effect, but this seems unlikely given that no dose-effect relationship was observed, and tachycardia has not been noted in previous studies. Other factors might have contributed to increased heart rate in our patient group, including anxiety, alcohol withdrawal and dehydration; however, the role of these could not be addressed directly by the present study.

Mirtazapine overdose was not associated with any significant prolongation of PR, QRS or QT intervals, suggesting that cardiotoxicity is not a feature. This is reassuring because other antidepressants have been found to have cardiotoxic effects in overdose. For example, tricyclic antidepressant ingestion is associated with prolonged QRS duration and increased risk of potentially fatal arrhythmias (13). Recent safety concerns have been raised in view of the emerging cardiotoxic effects of venlafaxine, particularly in elderly patients and those with established vascular disease [14]. Venlafaxine ingestion causes prolongation of the QRS interval, and is associated with a substantially increased risk of arrhythmias and seizures, thought to be due to sodium channel blockade (15–18). In one of our patients, a short-lived asymptomatic episode of supraventricular tachycardia was observed during cardiac monitoring. This is likely to have been a coincidental finding because there were no other features of toxicity, and it is commonly a benign and asymptomatic finding in young people (19).

An earlier study showed that venlafaxine overdose caused seizures in 13.7% of patients, compared to 3.5% for tricyclic antidepressants ($p < 0.01$) and 1.3% for SSRIs ($p < 0.001$); overdose with venlafaxine had an odds ratio for seizures of 4.4 (1.4–13.8) versus tricyclic antidepressants ($p = 0.009$) (12). The present study found no evidence of increased seizure risk after mirtazapine ingestion, and had 87% power to detect a 3% risk of seizures, assuming a background frequency of 0.1%. Given the study size, the true rate of seizure could be as high as 2.6%, assuming 95% confidence intervals.

Overall, our findings suggest that mirtazapine ingestion is associated with only mild clinical features. There were no significant adverse effects on any of the clinical, laboratory or ECG variables studied, and no specific treatment was required, apart from those required by patients with concomitant disease or who had co-ingested other drugs. A number of clinical reports of patients who have taken a mirtazapine overdose have been published previously, which suggest that it is comparatively non-toxic (20–29). Two patients presented with drowsiness and miosis, mimicking the effects of possible opiate ingestion (21). In two patients that ingested 30–50 times the normal daily dose, plasma concentrations 100–500 times higher than normal, but no significant toxic features were noted (22). A patient that ingested mirtazapine 375 mg, and had a plasma concentration 10–25 times higher than normal, had sinus tachycardia but no other toxic features (23). One patient is reported to have ingested mirtazapine 1200 mg and lorazapam 20 mg, and presented with reduced conscious level, hypothermia and rhabdomyolysis, and required invasive ventilation but made a full recovery (27). Rhabdomyolysis has been reported elsewhere after mirtazapine overdose and during therapeutic use, which was self-limiting in both cases (28,29). One published case describes a successful suicide attempt in a patient who had ingested mirtazapine, sertraline and amitriptyline in combination, although the mode of death was uncertain (30).

Based on our experience of treating these 117 cases, we propose that patients presenting to the Emergency Department after ingesting mirtazapine alone are unlikely to develop toxic features beyond 4 hours post-ingestion, and such patients could be considered for discharge home after this period providing that an appropriate psychiatric evaluation has been undertaken. Patients who have ingested mirtazapine in a mixed drug overdose are at greater risk of adverse effects and should be observed for clinical features of toxicity, which will depend predominantly on the co-ingested agent. Co-ingestion of alcohol, benzodiazepines or opioids exacerbates the sedative effects of mirtazapine and can be associated with significant respiratory depression.

A key limitation of the study is that the lack of observed toxic features does not exclude the possibility of toxic effects of mirtazapine ingestion. With a sample size of 117 patients, the risk of serious toxicity might be as high as 2.53% within 95% confidence intervals. A further limitation is that estimation of the amounts ingested relied on the patients' own account, and plasma concentrations of mirtazapine were not available to confirm the extent of drug exposure. Nonetheless, the study sample was unselected, and likely to be representative of patients encountered in the everyday clinical situation elsewhere. Collection of data from different institutions would have been useful for confirming the generalizability of our findings to other patient populations.

Conclusions

Overall, these data are reassuring and do not raise any specific concerns over the use of mirtazapine in high-risk patient groups. They are consistent with emerging case reports and review articles that suggest mirtazapine is comparatively non-toxic in overdose.

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