

MIRTAZAPINE – RELATED DEATHS

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Aim

The aim of this study was to evaluate the toxicological significance of the concentration of mirtazapine and its N-desmethyl metabolite (normirtazapine) in post-mortem blood in a series of deaths reported to HM Coroner.

Introduction

Mirtazapine is a novel tetracyclic antidepressant drug which has a complex pharmacological action on both noradrenergic and serotonergic neurotransmitter systems. The drug has been on the US and European markets for about 10 years, but relatively few deaths associated with mirtazapine have been reported in the literature. Early studies have suggested that the drug has a low toxicity when taken in overdose and that any adverse effects were not life threatening. Post-mortem blood mirtazapine concentrations of up to 0.3 mg/L have been reported in cases where the drug is not implicated in the cause of death. There is also evidence to show that the drug undergoes post-mortem redistribution, which can make interpretation of findings in suspected fatalities more difficult to assess.

Until recently, relatively few deaths due to poisoning reported in UK have noted the presence of mirtazapine. However, since 2000 the presence of the drug in a number of reported mixed drug fatalities has increased dramatically, possibly because of increased prescribing. In the last 2 years (2001-2003) the Laboratory has investigated a total of 8 cases (5 male, 3 female) aged between 17 and 77 years where mirtazapine has been found to be present in significant concentrations, but generally in association with other drugs or alcohol.

Analytical Methods

Post-mortem blood mirtazapine and its desmethyl metabolite (normirtazapine) have been measured using reverse phase liquid chromatography with U.V.diode-array detection (HPLC-DAD). The limit of detection of the method was 0.1 mg/L. In addition, extensive screening of blood and other fluids by immunoassay, also gas and liquid chromatography, was undertaken to determine the presence of other drugs and alcohol

Case Results (8 Fatalities between 2001-2003)

Case	Age	Sex	Site of Specimen	Mirtazapine Conc ⁿ (mg/L)	Normirtazapine Conc ⁿ (mg/L)	Mirtaz./Normirtaz. Ratio	Circumstances. Other Drugs Present and Concentrations (mg/L)
1	75	M	Femoral	2.2	0.3	7.3	Found dead at home. Temazepam (2.2) Venlafaxine (3.6)
2	46	M	Femoral	2.0	<0.1	>20	Found dead at home. Temazepam (1.1) Ethanol (214 mg/dL)
3	60	M	Unknown	1.6	0.8	2.0	Found dead in river. No other drugs detected.
4	56	M	Femoral	1.0	0.3	3.3	Found dead at home. Diazepam (1.5) Sildenafil (trace) Ethanol (72 mg/dL)
5	77	M	Femoral	2.1	1.1	1.9	Found dead in bed. Zopiclone (1.6)
6	51	F	Femoral	2.5	0.4	6.7	Found dead in the bath. Zopiclone (1.7) Lorazepam (0.4) Chlorpromazine (trace) Ethanol (54 mg/dL)
7	21	F	Common Iliac	1.3	0.3	5.0	Found dead at home. Dextropropoxyphene (2.4) Paracetamol (124) Venlafaxine (1.4) Zolpidem (trace)
8	17	F	Femoral	4.4	0.7	6.1	Found dead at home with suicide note. Diltiazem (4.2) Paracetamol (70) Zopiclone (trace)

Conclusions

- Mirtazapine appears to be more commonly seen in recent drug related fatalities, but this may be due to an increased prescribing of this antidepressant in the UK.
- Mirtazapine overdose appears to be a significant factor in at least half the deaths reported. In all but one case, other drugs or alcohol were present.
- Mirtazapine related fatalities appear to be associated with a parent femoral blood mirtazapine concentration of >2.0 mg/L and ratio of blood mirtazapine to normirtazapine concentration > 20.
- It is possible that a pharmacological interaction between mirtazapine, when present in high concentrations in overdose, and the presence of other drugs, may be the cause of the reported fatalities. But the mechanism of toxicity is uncertain.

References

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