

POST-MORTEM CASES INVOLVING DULOXETINE

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LGC Forensics

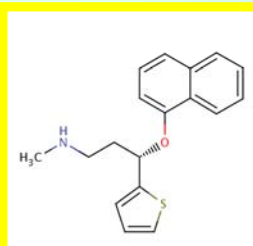
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INTRODUCTION

Duloxetine (Cymbalta®) is a selective serotonin and noradrenaline reuptake inhibitor (SSNRI) with weak activity on dopamine reuptake (1,2), prescribed for the treatment of major depressive disorder, generalised anxiety disorder, pain related to diabetic neuropathy, and stress urinary incontinence (3).

The aim of this work was to review five post-mortem cases, recently submitted to LGC Forensics for toxicological analysis, in which duloxetine, listed as one of the prescribed medications, was detected in the blood.



Pharmacology

Duloxetine is well absorbed following oral administration, with peak plasma levels occurring in 6-10 hours. It has an apparent volume of distribution of approximately 1640L, and an elimination half life of approximately 12 hours (range 8-17).

Therapeutic concentrations have been found to be in the range of 0.001 - 0.100 mg/L (4, 5, 6).

Elimination occurs mainly through hepatic metabolism involving two P450 isoenzymes, CYP1A2 and CYP2D6. The metabolites are primarily excreted into the urine in the form of glucuronide and sulphate conjugates (7).

The most common reported side effects encountered with duloxetine include nausea, headache, dry mouth, fatigue, insomnia, dizziness, somnolence, constipation and palpitations (3).

CASE DETAILS

Case 1 – 37-year old female: found dead in her bedroom. Recent history of self-inflicted injuries.

Prescribed medication: duloxetine (Cymbalta® 60mg daily), olanzapine (20mg daily), chlorpromazine (25mg daily), zopiclone (7.5mg daily), diazepam (dose unknown).

Case 2 – 42-year old female: found dead at home. History of depression.

Prescribed medication: duloxetine, amitriptyline, chlorpromazine, diazepam, flupentixol, ibuprofen, nitrazepam, tramadol.

Case 3 – 29-year old male: found hanged. History of depression and mental illness.

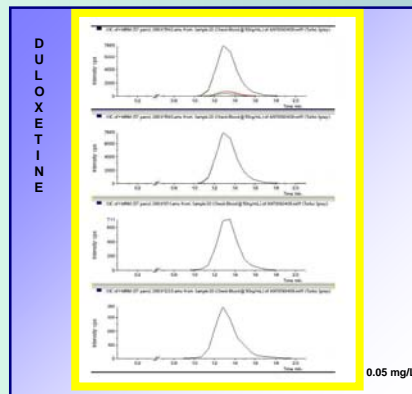
Prescribed medication: duloxetine, lithium, risperidone.

Case 4 – 60-year old male: found dead with a suspected self-inflicted gunshot wound.

Prescribed medication: duloxetine, levothyroxine, minocycline, mirtazapine.

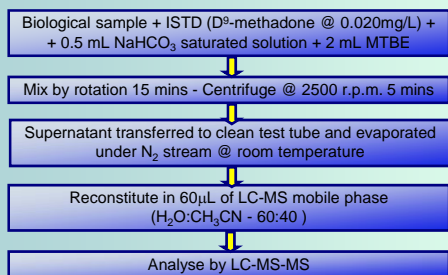
Case 5 – 56-year old female: found drowned. History of depression.

Prescribed medication: duloxetine, promethazine, zopiclone, reboxetine.



MATERIAL & METHODS

Duloxetine concentrations in blood samples were determined by LC-MS-MS following a liquid-liquid extraction as reported in the following scheme (calibration range 0.001 - 0.500 mg/L).



LC-MS conditions

- > LC: 1100 Agilent HPLC + Agilent 1100 Thermo autosampler + Agilent 1100 LC quaternary pump
- > MS: Applied Biosystems Q Trap 2000 mass spectrometer (turbo spray mode)
- > Triple quadrupole mass spectrometer: API source (turbo spray needle 5000V; nebulizer gas @ 40psi) + channel electron multiplier (CEM) detector in positive ion detection mode (heater in the source @ 500 °C)
- > COLUMN: Phenomenex 'Gemini' C18 column, 110A (150mm x 2.0mm i.d., 5µm) + Phenomenex 'Security Guard' cartridge ('Gemini' C18 4 x 2.0mm)
- > MOBILE PHASE: 1.2mM CH₃COONH₄ with 0.05% HCOOH in deionised H₂O/0.05% HCOOH in CH₃CN (60:40)
- > FLOW RATE: 350µL/min
- > COLUMN TEMPERATURE: 23°C
- > INJECTION VOLUME: 10µL
- > PRECURSOR ION FRAGMENTATION COLLISION GAS: ultra high purity nitrogen @ 20 psi, collision energy 14eV.
- > SCANNING: MRM mode
- > TRANSITION IONS: duloxetine m/z 298.10/154.02, 298.10/97.08, 298.10/123.02;

Preliminary tests carried out by GC-MS showed a low sensitivity for duloxetine, the limit of detection being approximately 1 mg/L. This technique was used to determine the concentration of duloxetine in the samples from Case 1, after simple dilution of the samples in ethanol.

RESULTS

Toxicological investigations were carried out according to customer requests. Results and toxicological interpretation are summarised in the following table.

	Duloxetine (mg/L)			Other findings of toxicological interest	Toxicological interpretation
	Blood	Urine	St. c.		
Case 1	0.91	0.67	1800	Blood: olanzapine 0.37 mg/L; chlorpromazine 0.28 mg/L; diazepam 0.034 mg/L; nordiazepam 0.035 mg/L; temazepam and oxazepam (low concentration); zopiclone 0.011 mg/L; salicylic acid Stomach contents: chlorpromazine 600 mg/L; olanzapine detected Urine: chlorpromazine detected; olanzapine detected	Duloxetine: higher than levels reported in literature Olanzapine: higher than normal therapeutic range High concentration of duloxetine and chlorpromazine in stomach contents Possible overdose
Case 2	0.034	-	-	tramadol 3.7 mg/L; methadone 0.6 mg/L; EDDP; amitriptyline 1.2 mg/L; nortriptyline 1.3 mg/L; codeine 0.08 mg/L; diazepam 0.13 mg/L (approx); nordiazepam (low concentration); paracetamol; β-hydroxybutyrate 112 µmol/L;	Duloxetine: therapeutic Amitriptyline, nortriptyline, codeine, paracetamol, diazepam: therapeutic (post-mortem redistribution) BHB level: normal Tramadol, methadone: may prove fatal in non-tolerant individuals Significant CNS depressant effects expected
Case 3	0.054	-	-	alcohol <10 mg/100mL; risperidone (low concentration) no lithium detected	Duloxetine: therapeutic Risperidone: therapeutic
Case 4	0.034	-	-	mirtazapine 0.054 mg/L (approx)	Duloxetine: therapeutic Mirtazapine: therapeutic
Case 5	0.069	-	-	Alcohol < 10 mg/100mL	Duloxetine: therapeutic

References

- Sharma A, Goldberg MJ and Cerimale BJ. Pharmacokinetics and safety of duloxetine, a dual-serotonin and norepinephrine reuptake inhibitor. *J Clin Pharm.* 2000; 40:161-167.
- Wong DT, Bymaster FP, Mayle DA, Reid LR, Kushtinski JH and Robertson DW. LY248686, a new inhibitor of serotonin and norepinephrine uptake. *Neuropharmacology.* 1993; 32:1-23-33.
- British National Formulary.
- <http://ip.illy.com/italy/cymbalta-pi.pdf> (06/2008 Revision)
- Lanz RJ, Gillespie TA, Rash TJ, Kuo F, Skinner M, Kuan H-Y and Krauder MP. Metabolism, excretion and pharmacokinetics of duloxetine in healthy human subjects. *Drug Metab Dispos.* 2003; 31:1142-1150.
- Waldschmitt C, Vogel F, Maurer C and Hemke C. Measurement of Duloxetine in blood using high-performance liquid chromatography with spectrophotometric detection and column switching. *Thin Layer Chromatogr.* 2007; 29(6):767-772.
- Dugin SE and Fuller MA. Duloxetine, a dual reuptake inhibitor. *Ann Pharmacother.* 2004; 38:2078-2085.
- Isalberti C and Reed D. Case study: a fatality involving duloxetine. *TIATF Bulletin.* 2006; 38(2).

CONCLUSIONS

Duloxetine is a relatively new antidepressant medication, introduced in the British National Formulary in 2005. In the recent months an increasing number of Coroner's cases in which duloxetine was mentioned among the prescribed medications have been recorded in our laboratory (6 cases in a period of 8 months; one was negative for duloxetine, indicating possible non-compliance, and was therefore not reported in the present work).

Of the five cases described in which duloxetine was detected, four had concentrations that were felt as post-mortem therapeutic levels. In Case 1 the concentration of duloxetine appeared to be significantly higher than those recorded in the scientific literature and the verdict at the inquest stated that it was "more likely than not" that the deceased had taken an overdose of duloxetine (8).

Considering a possible increase in the prevalence of duloxetine prescription, further investigation is required to gain a better understanding of the post-mortem behaviour of this drug. The possible effect of post-mortem redistribution and the potential role of duloxetine in deaths, particularly when taken in combination with other drugs, are of particular concern.

Also, in our experience, the possibility that routine screening procedures (particularly GC-MS in SCAN mode) might not detect duloxetine, unless present at a very high concentration, should be considered.