On an engaged case of cardiac arrhythmia following duloxetine intoxication

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Abstract: Background. At present, few studies have reported on acute or lethal intoxication after duloxetine ingestion; in almost all cases, the drug has been associated with other substances.

Objective. The present paper reports the case of a 65-year-old man suffering from a psychiatric disorder, who is under treatment with Cymbalta®. Despite no history of suicide attempts, his wife found him unresponsive in his bedroom near to an empty drug box.

Results. Toxicological analyses performed on post-mortem specimens revealed the presence of duloxetine at concentrations of 3.6, 7.3 and 63.4 µg/mL in his blood, bile and gastric content, respectively, and of 1.3 and 0.5 µg/g in his liver and brain. The cause of death was ascribed to cardiac arrhythmia following duloxetine intoxication.

Conclusions. Obtained data suggest possible cardiac arrhythmia related to DLX intoxication, and confirm the wide variability of toxic/lethal duloxetine concentrations reported in the literature, as well as the hypothesis of a non-linear elimination kinetics after massive drug intake.

Key Words: duloxetine, lethal intoxication, cardiac arrhythmia, suicide.

INTRODUCTION

Usually, moderate to severe depression is pharmacologically treated with antidepressant medications, e.g., selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs). Duloxetine, a fourth-generation SNRI (characterised by weak activity on dopamine reuptake and low affinity toward serotonergic, cholinergic, adrenergic and histaminic receptors), is widely used for the treatment of major depressive disorder [1-6]. Manufactured by Eli Lilly Inc. (Indianapolis, IN, US), duloxetine hydrochloride (DLX) [Cymbalta®, (+)-(S)-N-methyl-γ-(1-naphtyloxy)-2-thiophenepropylamine hydrochloride] was approved by the U.S. Food and Drug Administration in September 2002 for the treatment of major depressive disorder (MDD). It was subsequently approved in September 2004 for the treatment of pain associated with diabetic peripheral neuropathy; moreover, the Yentreve® formulation has been approved in Europe for anxiety disorders, and is recommended as an adjunct medication for stress urinary incontinence in lieu of surgery [7, 8].

Duloxetine is not structurally related to other tricyclic antidepressants (TCAs), nor to monoamine oxidase inhibitors; rather, its structure consists of a secondary amine (molecular weight: 297 g/mol; empirical formula: C18 H 19 NOS). DLX is administered as capsules containing 20, 30 or 60 mg of active agent in enteric-coated pellets. Recommended doses vary based on the disorder: 40–60 mg/day are normally administered for depression,
while 60 mg/day are administered for neuropathic pain and 80 mg/day for stress urinary incontinence [7]. In the US, psychiatrists tend to use a higher dose for longer periods for the treatment of severe depression [9].

Following oral administration, DLX is well absorbed, with an absolute bioavailability of 32–80%; peak plasma concentrations are reached 6 h (t max) post dose. Concomitant food intake may cause a delay in t max by 4 h, up to 10 h [6]. Duloxetine is distributed extensively throughout the body, and the apparent volume of distribution averages approximately 1,640 L [6]; the elimination half-life varies between 8 and 17 h (mean 12 h) [10]. DLX is metabolised by two P450 isoenzymes (CYP1A2 and CYP2D6), with initial oxidation of the naphthyl ring, followed by further oxidation, methylation, and/or conjugation [7, 10, 11]. Metabolites are mainly excreted in the urine as glucuronide and sulphate conjugates (72%) or in the faeces (18.5%), while less than 1% of the absorbed dose is excreted unchanged in the urine.

Duloxetine administration is associated with headache, nausea, memory impairment, somnolence and hyponatremia, dry mouth, constipation, fatigue and slight increase in blood pressure (especially when the subject is in a supine position), as well as a slight decrease in heart rate [12, 13]. Although reported, cardiovascular effects do not seem to be clinically significant [14]. Ball et al. reported a mean increase of 0.95 mmHg in diastolic blood pressure, while systolic pressure remained unchanged [15]. The analysis of pooled data from eight placebo-controlled clinical trials showed safety and tolerability of DLX [16]. According to Ball et al.’s conclusions, treatment with DLX (60 mg/day) did not involve significant changes in haematology or blood chemistry laboratory values [15]. However, possible hyponatremia with consciousness alterations are reported among the adverse effects highlighted for DLX [7].

Because of the potent serotonin-reuptake inhibition of duloxetine, potentially fatal serotonin toxicity may occur when DLX is administered in the presence of other pro-serotonergic agents [17]. Death has been attributed to a dosage of about 4 mg or more of duloxetine hydrochloride [17, 18]. A dosage of 60 mg or less per day results in generally mild, transient and less common adverse effects, and the influence of sex, gender and race on experienced adverse effects is minimal at such a dosage level. Symptoms associated with overdose (either attributable to DLX alone or with mixed drugs) include somnolence until coma, serotonin toxicity, seizures, syncope, tachycardia, hypo- and hypertension, and vomiting.

Considering the expanding scope of approved indications, there has been an increase in fatal cases in which duloxetine has been identified: according to the annual reports of the American Association of Poison Control Centers, a single case was reported in 2004, five in 2005, 11 in 2006 and 14 in 2007 [19]. Pilgrim et al. reported the prevalence of duloxetine in coronial cases during the period 2009–2012; duloxetine was detected in 34 cases, out of which 19 were attributed to drug toxicity [17]. In many cases, the concomitant use of numerous medications was reported; up to 13 other drugs were co-detected in a single case, and only in four cases did death involve duloxetine alone. Despite this, there is a paucity of data on duloxetine levels in post-mortem specimens, especially when it is the only drug involved in potential fatal intoxication [7, 8, 17–22]; indeed, the importance of reporting data on post-mortem DLX levels is stressed by different researchers [8, 20]. In this respect, the present paper reports a case of fatal intoxication in a 65-year-old man, following massive duloxetine intoxication.

**CASE REPORT**

A 65-year-old man was found unresponsive in his bedroom by his wife in the early morning, no CPR and lithium administration were attempted. Inspection of the death scene revealed the presence of an empty drug box, meant to contain 30 mg of duloxetine (a 28-capsule capacity blister pack). His past medical history included hypertension, depressive anxiety disorders and psychotic bipolar syndrome. The decedent was no smoker, his weight was 70 kg and the man was undergoing pharmacological treatment with Cymbalta* (prescribed dosage: 60 mg/day). His wife declared that the drug box was acquired two days before the death. The autopsy was performed two days after death; peripheral blood was collected from femoral vein prior to opening the body. Encephalic and acute pulmonary oedema were evidenced. The heart was 380 g and a pronounced left ventricular hypertrophy was present (thickness of the wall was 1.5 cm).

**Histological analysis**

Specimens of the brain, lungs, heart, liver, kidney and muscle tissue were sampled during autopsy and prepared and stained with H/E. Sections 2–3 µm thick were cutted and evaluated by light microscopy, using a D.M.R. Leica microscope from Leica Microsystems (Wetzlar, Germany). From each section, four to five visual fields were randomly selected.

**Histological findings**

**Brain.** Nervous tissue was well organised, and both neurons and glial cells were well stained. Pericellular and perivascular spaces presented enlarged, thus presenting like vacuoles. Cerebral vessels were congested.

**Heart.** Myocardial fibres showed marked hypertrophy and resulted fragmented; the interstitial spaced appeared enlarged. Nuclei were well evident and increased in size (see Fig. 1).

**Lungs.** The alveolar structure was well visible, with abundant eosinophilic material within alveolar cavities; septa were thickened and oedematous, and vessels were

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61
congested (see Fig. 2).

Liver. Hepatic tissue presented enlarged sinusoids and central veins, indicating acute stasis.

Kidney. Glomerular population was well represented. Tubular tissue was degraded with presence of amorphous material within the lumen.

Muscle tissue. Muscle tissues were normally represented and the fibres showed good organisation, resulting properly stained.

Toxicological analyses

Duloxetine hydrochloride and carbinoxamine maleate were purchased from Santa Cruz Biotechnology (Dallas, TX, US). All other solvents and reagents were from Carlo Erba (Milan, Italy). Gas chromatographic/mass spectrometric analyses (GC/MS) were performed using a FocusGC chromatographer connected to an AS 3000 autosampler and a DSQII single quadrupole mass spectrometer (ThermoElectron Corporation - San Jose, CA, USA). For the gas chromatographic separation, a Rxi®-5MS (30m x 0.25mm x 0.25µm) capillary column from Restek (Bellefonte, PA, USA) was used. Data were acquired and processed by using Xcalibur software (2.0.7 version) from ThermoElectron.

Toxicological analyses were performed on body fluids (blood, bladder lavage and bile), gastric contents, and organ or tissue samples (liver, brain). Peripheral (femoral) blood samples were collected in vials containing sodium fluoride, while all other specimens were collected without preservatives; all samples were stored at -18°C until analysis. Solid tissue samples were homogenised after 1:1 dilution (w/v) with distilled water. Analysis of alcohol and volatiles was performed on peripheral blood samples by headspace-gas chromatography-flame ionisation detection (HS/GC-FID). Urine (bladder lavage, using 5 mL of bidistilled water) and blood samples were screened by immunochromatographic assay for common drugs of abuse (cocaine, opiates, cannabinoids, amphetamine/methamphetamine and derivatives, barbiturates, methadone, buprenorphine, phencyclidine, fentanyl, LSD,

Figure 1. Myocardial fibres evidenced hypertrophy; nuclei were well evident and increased in size (panel a, 10X). Panel b (20X, detail of previous panel) shows several fragmented fibres and an enlarged interstitial space.

Figure 2. Pulmonary tissue presented enlarged alveolar structure and diffuse oedema (panel a, 5X). Panel b (10X, detail of the previous panel) shows thickened septa and presence of pneumocytes and macrophages within alveolar spaces.
kemamine, oxycodone, prooxyphene, methaqualone). In particular, the Evidence Investigator (Randox, Crumlin, U.K.), a homogenous enzyme immunoassay, was used.

Both HS/GC-FID and immunoassay tests resulted negative with regard to screen analytes. Biological fluids and tissue homogenates were also screened for the presence of basic drugs after extraction with TOXI-LAB A cartridges (Varian Inc., US); organic extracts were analysed by GC/MS. GC/MS full scan analyses demonstrated the presence of duloxetine, which was then quantified in all biological specimens via GC/MS-SIM.

**Duloxetine GC/MS-SIM analysis**

A SIM mode was used for duloxetine quantification, selecting ions at m/z 115.0, 144.0 and 154.0 for DLX, and ions at m/z 58.0, 71.0 and 167 for the internal standard (I.S). Six calibrators in the 0.05–3.0 µg/mL range were prepared in duloxetine-free blood samples. Blood samples were spiked with DLX working stock solutions at 10 and 100 µg/mL prepared in methanol. Samples were added with 100 µL of a standard methanolic solution of carbinoxamine at 15 µg/mL, used as an I.S. [8] and purified by means of a liquid/liquid extraction. In particular, 2 mL of 20% Na₂CO₃ and 6 mL of Cl-butane were added, and the samples were vortexed and centrifuged (10 min at 4000 rpm). The organic layers were discharged. The aqueous phases were washed with 4 mL of n-pentane, and the samples were centrifuged and the organic layers discharged. The obtained aqueous phases were added with 4 mL of n-pentane, and the samples were centrifuged and the organic layers discharged. The obtained aqueous phases were added with 1 mL of 20% Na₂CO₃, and the samples were purified using 4 mL of n-pentane. The organic phases were transferred into clean test tubes and then dried under nitrogen stream. The samples were reconstituted with 100 µL of methanol and transferred to autosampler vials for GC/MS-SIM analysis.

Linear interpolation was applied, obtaining an R² greater than 0.998. Percentage DLX recovery was calculated by means of quality control samples at 0.25 (n=5) and 1.5 µg/mL (n=5), by comparing mean peak areas with the ones obtained for non-extracted samples at the same concentrations. Results highlighted a mean DLX recovery of 80%. Quality control samples at 0.25 and 1.5 µg/mL, prepared in DLX-free blood and analysed according to the previously described procedure, were used to evaluate the accuracy and the precision (in terms of CV%) of the analytical method, obtaining percentage values ranging from -1.3% to 0.5% and from 3.0% to 5.5%, respectively.

**Biological specimens** (2 mL aliquot of the fluid or homogenised organ) were spiked with the I.S. and purified as previously described for the calibrators. Case specimens with a DLX concentration exceeding the calibration curve range were diluted and re-processed. Table 1 summarises the obtained duloxetine concentrations.

**DISCUSSION**

Psychotropic drugs have proarrhythmic properties, and are able to induce a QTc prolongation (also when administered at low doses) as well as determine ventricular tachycardia due to altered repolarisation. Such a state is characterised by a QRS complex with variable amplitude and frequency in the range of 200–250 bpm, the so-called tordase de pointes. Wenzel et al. [23] reported the following risk factors that are able to induce QTc prolongation in subjects being treated with psychotropic drugs: age greater than 65 years, female sex, myocardial hypertrophy, congenital long Q-T syndrome, sinus bradycardia, fluid and electrolyte disorders, high plasmatic doses of the psychotropic drug, inhibition of drug metabolism by co-administered drugs, and reduction of drug clearance due to renal and/or liver failure. In the presently discussed case, several risk factors were present, including age, left ventricular hypertrophy and high plasmatic doses of DLX. Moreover, neither renal failure nor rhabdomyolysis was histologically evident. Based upon histological and toxicological findings, death was ascribed to possible cardiac arrhythmia following duloxetine intoxication.

Indeed, data from clinical trials following DLX administration at therapeutic doses did not highlight any effect on the QT interval. Despite this, in the presently reported case it seems reasonable to assume that the high DLX intake (likely 720 mg, corresponding to 24 Cymbalta® capsules) could result in lethal arrhythmia characterised by tordase de pointes. Recently, Mari et al. published a case report of acute duloxetine intoxication with fatal outcome; cause of death was ascribed to acute massive pulmonary thromboembolism [20].

Histological findings of the here reported case were unspecific, since data evidenced a generic cardiac hypertrophy only; however, they were in line with possible death from cardiac arrhythmia. Within such an assumption, hypertrophic myocardial fibres, pulmonary and cerebral oedema, and glomerular population without significant pathological alterations or any other aspect related to rhabdomyolysis or hyponatremia were evident.

Although duloxetine is normally considered a well-tolerated drug across all therapeutic ranges approved in adults [7], it must be stressed that its pharmacological-toxicological profile has not been fully elucidated [21]. Data indicate a mean plasma concentration of 0.013 µg/mL after a single 20-mg duloxetine dose [8]. Sharma et al. published a study based on eight subjects with DLX doses

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*N.D., not detected.
of 20, 40 and 60 mg, demonstrating a correlation between dose and plasma concentrations (mean reported value: 0.95 µg/L/mg, range: 0.38 to 1.89 ng/mL/mg) [12]. Anderson et al. used Sharma et al.’s dose/plasma concentrations proportionality constant to extrapolate plasma DLX concentrations after a known drug intake: daily doses of 60 and 120 mg would yield mean plasma concentrations of 0.057 µg/mL (ranging from 0.023 to 0.113 µg/mL) and 0.114 µg/mL (ranging from 0.046 and 0.227 µg/mL), respectively [8]. In the same study, based on results of twelve cases, the authors reported duloxetine post-mortem blood concentrations (central blood) between ‘Not Detected’ (N.D.) and 0.59 µg/mL. Concentrations detected in femoral blood levels ranged from N.D. to 0.26 µg/mL, thus evidencing duloxetine post-mortem redistribution. In seven out of the 12 cases, fatal outcome could not be related to drug intoxication, while the remaining five were related to suicidal (three) or casual (two) intoxications; all cases referred to multi-drug intoxication.

The measured post-mortem blood duloxetine concentration in the present case, 3.6 µg/mL, indicated an excessive drug intake, which was confirmed by drug levels detected in the bile, liver, brain and gastric contents (see Table 1). According to Sharma et al.’s dose/plasma concentration proportion constant (0.95 µg/L/mg), the obtained post-mortem blood levels (3.6 µg/mL) would correspond to the ingestion of a number of Cymbalta® capsules higher than those available, thus confirming the limits of such approach for a correct estimation of the absorbed dose.

In the here reported case DLX was the only detected drug, while the cited literature refers to multi-drug intoxication. Thus, this case study may represent a valid contribution for elucidating duloxetine’s toxicity profile, highlighting the need for particular attention regarding the treatment of older patients presenting renal and cardiac comorbidity.

**Conflict of interest.** The authors declare that they have no conflict of interest concerning this article.

### References