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The prevalence of duloxetine in medico-legal death investigations in Victoria, Australia (2009–2012)

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ABSTRACT

The drug duloxetine (Cymbalta®) is a newer antidepressant which has been available in Australia since 2008. Duloxetine is a serotonin and noradrenaline reuptake inhibitor (SNRI), which is associated with adverse effects in the first 6 weeks of therapy, including tachycardia and worsening symptoms in people with advanced heart failure. It is also associated with serotonin toxicity in combination with certain drugs. Few reports have been published in the toxicology literature regarding duloxetine and its prevalence in coroners' cases. This study documents the prevalence of duloxetine in coronial cases between 2009 and 2012 and seeks to better understand the role of duloxetine in deaths where concomitant use with other drugs may cause adverse outcomes. Duloxetine was analyzed in blood specimens taken for the purpose of assisting the pathologist in determining a cause of death and analyzed using a validated LC–MS/MS method employed for overnight screening. There were 34 cases where duloxetine was detected of which 19 were attributed to drug toxicity. The median femoral blood concentration in the cohort was 0.14 mg/L (range 0.01–1.42 mg/L). Many deaths involved the concomitant use of numerous other medications; up to 13 other drugs were co-detected in a case. Over half of the deaths were attributed to fatal combined drug toxicity. SSRIs and venlafaxine that may have increased the risk of serotonin toxicity in combination with duloxetine were detected in five cases. Metoclopramide, contraindicated with duloxetine use, was detected in two cases. NSAIDs ($n = 11$), antipsychotics ($n = 15$) and benzodiazepines ($n = 14$) were also commonly co-detected. Heart disease was observed in over 40% of the cohort, mostly in the form of coronary artery disease or cardiomegaly. Death involving duloxetine alone was uncommon ($n = 4$); however with certain comorbidities and co-administered drugs, the risk of a fatal event is increased, particularly in the setting of other pro-serotonergic agents. In deaths where duloxetine is detected and the cause of death is believed to be natural or unascertained, it is essential that other serotonin drugs or inappropriate drug combinations be examined for their possible contribution to death.

1. Introduction

Duloxetine (Cymbalta® (Australia), Yentreve®, and in parts of Europe, Xeristar® or Ariclaim®) is a serotonin and noradrenaline reuptake-inhibitor that is used in the treatment of major depressive disorder and generalized anxiety disorder. It also has regulatory approval for the management of a number of other CNS conditions, including diabetic peripheral neuropathic pain, fibromyalgia and stress urinary incontinence in women [1].

The most frequent adverse reactions to duloxetine occur in the first weeks of treatment and include nausea, headache, somnolence and other serotonin-mediated symptoms. The associated noradrenergic effects include mydriasis – a hazard for people with raised intraocular pressure or at risk of acute narrow-angle glaucoma – and a slight increase in heart rate and blood pressure [2,3]. The potent serotonin-reuptake inhibition of duloxetine can also cause potentially fatal serotonin toxicity (also known as serotonin syndrome) with co-administration of other pro-serotonergic agents [4–8].

Very few cases of duloxetine toxicity have been reported, of which most were non-fatal [9–12]. It is considered to be a relatively safe drug, with most deaths involving the concomitant use of other drugs. Indeed, there have been non-fatal, acute overdoses with duloxetine in clinical trials with doses as high as 1400 mg [3]. Menchetti and colleagues reported a non-fatal case of toxicity involving ingestion of over 500 mg of duloxetine [11]. Plasma concentrations were reported as 0.38 mg/L, with

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symptoms including confusion, dizziness and electrolyte imbalances.

Signs and symptoms of overdose (either with duloxetine alone or with mixed drugs) include somnolence, coma, serotonin toxicity, seizures, syncope, tachycardia, hypotension, hypertension and vomiting. Hepatic failure was noted in one death [9] and a more recent report described tachycardia and acute massive pulmonary thromboembolism due to acute intoxication by duloxetine [10]. A case of intentional fatal toxicity also involving baclofen reported a plasma concentration of duloxetine at 2.5 mg/L [12]. Baclofen was also quantified at concentrations usually associated with a toxic range. A further six duloxetine-associated deaths were reported by Vey and Kovelman, however the role of duloxetine in each of these cases was overshadowed by the presence of baclofen, natural disease, or the excessive use of potent prescription opioids [12].

There is very little published on duloxetine, including data on post-mortem toxicological drug concentrations and its involvement in drug-related fatalities. An assessment of the contribution of this drug is essential in understanding the role duloxetine plays in sudden or unexpected death, particularly when detected at concentrations usually associated with therapeutic use. The aim of this study was to determine the prevalence and blood concentrations of duloxetine in deaths reported to the Victorian State Coroner, Australia, in order to better understand the role of duloxetine in deaths where therapeutic use and concomitant use with other serotonin drugs may have caused adverse outcomes.

2. Methods

2.1. Case collection

Cases where duloxetine was detected during routine toxicological analysis at the Victorian Institute of Forensic Medicine (VIFM) were obtained by performing a search of the National Coronial Information System (NCIS), a storage and retrieval system for cases reported to a coroner in Australia since 2000.

VIFM began routine screening for duloxetine in 2009. Toxicological analysis involves preliminary drug screens using a semi-quantitative gas-chromatographic method [13] for a variety of common drugs and a conventional immunoassay on urine (CEDIA) and/or blood (ELISA) for drugs of abuse (Thermo Fisher Scientific, Australia). Identified drugs are subsequently confirmed using quantitative gas chromatography–mass spectrometry (GC–MS) or liquid chromatography–tandem mass spectrometry (LC–MS/MS) with a lower limit of quantitation at the low end of their respective blood concentrations when used therapeutically. Since 2009, a rapid screening LC–MS/MS method has been adopted in place of the older GC–MS methods, for the detection of about 150 of the most commonly used drugs in Australia.

A search was performed for all cases occurring in the state of Victoria between 1 January 2009 and 31 December 2012. Case demographics including age, gender, circumstances of death together with autopsy and toxicology reports, mental illness and other comorbidities, police reports and coronial findings where present, were accessed using the NCIS.

All blood specimens were collected from the femoral region and were analyzed using validated methods in the accredited forensic toxicology laboratory at the VIFM.

2.2. Data analysis

Each death was assessed individually for the post-mortem concentration of duloxetine and any other co-detected drugs, in particular those drugs that can interact with duloxetine. Cases where drugs were detected at concentrations usually associated with therapeutic use were examined more closely for possible drug interactions and assessed using the Micromedex®2.0 database [14].

The circumstances in which the death occurred were examined in the coroners' findings. Pathology reports were examined for information that may be relevant to the death, including the presence of natural disease.

2.3. Ethical review

This research study was approved by the Victorian Institute of Forensic Medicine Ethics committee and the Department of Justice Human Research Ethics Committee. Special approval was granted by the Victorian State Coroner to access the 16 cases still under investigation at the time of publication.

3. Results

3.1. Characteristics of cohort

The cohort consisted of 34 cases (53% males) (Table 1). Most deaths were attributed to drug toxicity (19 cases). Heart disease was observed in over 40% of the cohort, mostly in the form of coronary artery disease (9 cases, median 57 years old) or cardiomegaly (4 cases, median 54 years old). Lung pathology including pulmonary edema (3 cases) was also seen in almost a third of cases (Table 2).

Over 35% of the cohort involved intentional self-harm, however 18% of cases were still under investigation by the coroner thus manner of death could not be established. Of the three accidental deaths, one was attributed to drug toxicity involving benzodiazepines, opioids and quetiapine (Case 5). The other two were deaths attributed to choking on a food bolus involving co-administration of antipsychotics (Case 29) or cardiac medications (Case 32).

3.2. Duloxetine and other drugs

The median concentration of duloxetine in the cohort was 0.14 mg/L, ranging between 0.01 and 1.42 mg/L. The case involving 1.42 mg/L was a case of intentional self-harm with death attributed to combined drug toxicity (Case 19).

The median concentration of duloxetine seen in the cases attributed to natural disease was 0.18 mg/L, which was higher even than the median duloxetine concentration in the cases attributed to drug toxicity (0.14 mg/L). It was lowest (0.082 mg/L) in the group attributed to external injury.

There were a number of cases involving drug combinations that may have increased the risk of toxicity (Table 3). Two cases involved the co-administration of metoclopramide, while 5 cases involved concomitant use of serotonin reuptake-inhibitors. Other weaker pro-serotonergic agents were observed, including oxycodone ($n = 5$), fentanyl ($n = 1$) and mirtazapine ($n = 2$).

There were a further 11 cases involving the use of non-steroidal anti-inflammatory drugs and 5 cases involving a moderate risk of drug interaction with the use of tricyclic antidepressants (TCA) or warfarin. Other commonly detected drugs included antipsychotics (44%), with quetiapine detected in 11 cases, as well as benzodiazepines (44%).

There were 4 cases where duloxetine was detected in the absence of any other drug/s, of which 1 was a case of drug toxicity with a blood concentration of duloxetine at 0.185 mg/L, while the other 3 were external injury deaths with incidental levels of duloxetine.