

Two Fatalities Involving Pregabalin

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INTRODUCTION

Pregabalin, manufactured by Pfizer and marketed under the trade name of Lyrica®, is indicated for the treatment of neuropathic pain, epilepsy and generalised anxiety disorder [1]. It was approved in the European Union in 2004. It is available as hard capsules containing doses ranging from 25 to 300mg, each marked with PGN followed by dosage (Figure 1). The maximum daily dosage is 600mg.



Figure 1. Capsules containing 100, 150, 200 and 300mg Pregabalin (TICTAC Communications Ltd)

Pregabalin (Figure 2) is a novel, structural, gamma-aminobutyric acid (GABA) analogue. Like gabapentin, it acts upon the alpha(2)delta subunit protein of voltage gated calcium channels, resulting in the decrease in the synaptic release of several neurotransmitters including glutamate, noradrenaline, serotonin, dopamine and substance P. However, it is a more potent successor to gabapentin, with effective doses being 3-10 times lower [2].

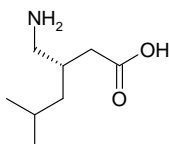


Figure 2. The chemical structure of pregabalin

PHARMACOKINETIC PROPERTIES

Oral Bioavailability: >90%

Oral Distribution: 0.56L/kg

Cmax: 1hr (2.5hr with food)

Steady State: 24-48hr (repeat dosing)

Half Life: 6.3hr (directionally proportional to creatinine clearance)

Absorption: L-aminoacid transport system (capacity limited)

Metabolism: Insignificant in humans

Elimination: Approx 98% unchanged in urine

Protein Binding: Minimal

Activity at Cytochrome P450: No

Drug Interactions: None known to date

Electronic Medicines Compendium

CASE STUDY 1

In March 2009 a 49 year old female (BMI 23.5) presented to the emergency department with upper gastrointestinal bleeding and haematemesis. She was admitted for further investigation. Two days later, she was discovered with her eyes locked in a downward fixed stare with abnormal, decerebrate, posturing and a GCS of 9. A search of her handbag revealed used blister packets of zopiclone, diazepam and pregabalin, which had been prescribed 5 days previously. The empty blisters would have amounted to 105mg, 245mg and 3150mg, respectively, if they had been ingested simultaneously. As she had a history of psychiatric illness and previous attempts of self-harm, concern was raised regarding overdose. Naloxone proved ineffective. Her blood pressure and heart rate (38bpm) dropped and her oxygen saturation fell to 40% on oxygen. Despite further life saving attempts she was declared dead approximately two hours after her initial discovery.

Post-mortem examination revealed multiple healed scars on her left forearm and a few on her right, consistent with previous self-harm attempts. No natural disease was present to explain death, other than pulmonary oedema which developed in the terminal stages.

CASE STUDY 2

In May 2009 a 50 year old male (BMI 35.1) was found dead in bed surrounded by empty medication packets of pregabalin, gabapentin, diazepam, venlafaxine, amitriptyline and simvastatin. He was a known schizophrenic with a past medical history of alcohol and benzodiazepine dependency, psychogenic non-epileptic seizures and depressive disorder.

At post-mortem examination there were signs of decomposition. The heart and liver were large in size. The liver was greasy and fatty. There was no evidence of significant injury or acute natural disease.

TOXICOLOGY

In case studies 1 and 2, unpreserved post-mortem femoral blood and unpreserved post-mortem femoral blood and urine, respectively, were submitted to the laboratory for analysis. Systematic toxicological analyses revealed the presence of:

Case Study 1: Cyclizine (<0.1mg/L), Diazepam (0.26mg/L) Nordiazepam (0.21mg/L), Temazepam (0.01mg/L), Oxazepam (0.01mg/L), Morphine (0.08mg/L), Zopiclone (0.24mg/L) and **Pregabalin (25.3mg/L)**.

Case Study 2: Ethanol (BL: 44mg/dL, UR: 69mg/dL), Ethyl glucuronide, Amitriptyline (0.56mg/L), Nortriptyline (0.16mg/L), Diazepam (0.51mg/L) Nordiazepam (0.37mg/L), Temazepam (0.03mg/L), Oxazepam (0.02mg/L), Venlafaxine (6.3mg/L), Gabapentin* (8.8mg/L) and **Pregabalin* (180mg/L)**.

*Analysis undertaken by The Medical Toxicology Laboratory. Pregabalin methodology has been described previously [3].

DISCUSSION

Pregabalin is a new drug and very little information is available regarding therapeutic serum/plasma concentrations. One report states that in samples collected at random times relative to dose from patients maintained on 600mg/day, plasma pregabalin concentrations ranged from 0.9-14.2mg/L [4]. Within the normal dose range there is a linear relationship between dose and plasma level. Review of the scientific literature revealed only two reports of pregabalin overdose [5,6]. The first case was a self poisoning involving both lamotrigine and pregabalin, which required significant intensive care support. This report documented the highest plasma concentrations of lamotrigine ever recorded in the literature, and the symptoms were primarily attributed to this drug. In the second case a pregabalin concentration of 29mg/L was detected, 9 hours post-ingestion, with a benign outcome. To date there are no reports of pregabalin related fatality. The extent of post-mortem redistribution of pregabalin is unknown and this should be considered when attempting to apply therapeutic serum/plasma concentrations to the interpretation of post-mortem blood concentrations.

CONCLUSION

In case 1, the pathologist attributed the cause of death to pregabalin and zopiclone toxicity. In case 2 the cause of death was attributed to mixed drug poisoning, primarily venlafaxine and pregabalin. In both cases there was supporting evidence of excessive pregabalin consumption.

REFERENCES

- [1] Lyrica Capsules – Electronic Medicines Compendium (eMC). <http://emc.medicines.org.uk/>
- [2] Stefan H and Feuerstein TJ. Novel anticonvulsant drugs. *Pharm & Therap.* 2007;113:165-183.
- [3] Berry D and Millington C. Analysis of pregabalin at therapeutic concentrations in human plasma/serum by reversed-phase HPLC. *Ther Drug Monit.* 2005 Aug;27(4):451-6.
- [4] Arroyo S, Anhut H, Kugler AR, et al. Pregabalin add-on treatment: a randomised, double-blind, placebo-controlled, dose-response study in adults with partial seizures. *Epilepsia.* 2004;45:20-27.
- [5] Braga AJ, Chidley K. Self-poisoning with lamotrigine and pregabalin. *Anaesthesia.* 2007 May;62(5):524-7.
- [6] Spiller HA, Bratcher R and Griffith JR. Pregabalin overdose with benign outcome. *Clin Toxicol (Phila).* 2008 Nov;46(9):917.