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Pregabalin concentrations in post-mortem blood—A two year study

Jane A. Eastwood *, Elizabeth Davison

LGC, Toxicology Department, Queens Road, Teddington, Middlesex TW11 0LY, United Kingdom

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ABSTRACT

Pregabalin (PRG) is indicated for the treatment of neuropathic pain, epilepsy and generalised anxiety disorder. Limited data exists on reference blood concentrations for this drug and levels above which death can be attributed to PRG toxicity. Furthermore, there is increasing evidence that the drug is subject to abuse. This study reviews the post-mortem blood concentrations of PRG analysed in the authors' laboratory between 2012 and 2014 in order to try and assign the likely therapeutic and fatal ranges. PRG was detected in 70 post-mortem blood samples of which 33% were at concentrations considered to be in excess of the reference range (above 17 mg/L). PRG concentrations ranged from 0.05 mg/L to 226 mg/L (median 8.0 mg/L) in the group as a whole and in one case a PRG concentration of 76 mg/L was determined to be the likely cause of death as no other drugs of significance were involved. The results from this study are consistent with the scientific literature with respect to a high frequency of multidrug use, particularly with opioids/opiates which can increase the probability of a fatal outcome.

1. Introduction

PRG is a medicinal drug which is approved for the treatment of neuropathic pain, epilepsy and generalised anxiety disorder. It was licensed in 2004, under the brand name Lyrica®, and is available on prescription in the European Union and the United States. The recommended dosage is 50–200 milligrams 2 or 3 times daily [1]. PRG can be administered with opioids for severe pain conditions, and is well tolerated in combination with other antiepileptic drugs [2–4].

PRG is a chemical analogue of the inhibitory neurotransmitter, gamma-amino butyric acid [5]. Side effects of PRG are reported to include euphoria, asthenia, dizziness, drowsiness, ataxia, confusion and blurred vision. High doses have resulted in seizures, reduced consciousness, tachycardia and ultimately death [6].

In recent years, PRG has started to be abused due to its euphoric effects, rapid absorption and fast onset of action [7–12]. Effects are described by abusers as comparable with alcohol/benzodiazepines/GHB but with enhanced euphoria. Furthermore, PRG is reported to assist in coping with opioid withdrawal [8]. Abuse of high PRG doses has become increasingly common and fatalities have occurred, particularly when combined with opioid/opiate drugs [8,11]. In the vast majority of cases reported in the literature, PRG has been detected in combination with at least one other drug, most commonly opioids/opiates, benzodiazepines and antidepressants, and is frequently encountered in drug dependant individuals [7].

The mechanism of toxicity is believed to be central nervous system depression with respiratory failure and cardiac complications [8]. Serotonin syndrome has been observed when pregabalin is used with an opioid [13]. Pathologist's referrals indicate that PRG deaths are often delayed and therefore post-mortem concentrations may not represent peak concentrations of the drug [8].

Therapeutic plasma concentrations for a 150 mg/day dosage are reported to range from 0.29 to 2.84 mg/L (median 1.27 mg/L) [2], and from 0.87 to 14.2 mg/L (median 4.88 mg/L) for a 600 mg/day dosage [16]. Post-mortem blood concentrations of PRG in individuals prescribed the drug were reported to range from 0.4 to 17 mg/L (median 5.6 mg/L) in femoral blood, and 1.5 to 11 mg/L (median 4.6 mg/L) in heart blood [11]. Within the usual therapeutic dose range, there is a linear relationship between dosage and plasma concentrations [16]; however, the blood to plasma/serum ratio has not been documented.

The extent of post-mortem redistribution has not been studied but it has been reported to be minimal, irrespective of the concentration and based on less than three days between death and sampling [11].

There are few reports of PRG toxicity being the primary cause of death, however one reported death attributed solely to PRG toxicity (with the presence of therapeutic levels of diazepam and temazepam and traces of quetiapine, levopromazine and ethanol)

* Corresponding author.
E-mail addresses: Jane.eastwood@lgcgroup.com (J.A. Eastwood), lizziedavison@hotmail.co.uk (E. Davison).

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had a PRG blood concentration of 110 mg/L [8]. Another report of two fatalities presented with significantly different PRG concentrations in whole blood of 25.3 mg/L (in combination with zopiclone) and 108 mg/L (in combination with a mixture of other drugs, primarily venlafaxine [17].

The aim of the present study was twofold; firstly to review PRG concentrations measured in post-mortem blood by the authors' laboratory and compare with the existing reference ranges and consider concentrations at which PRG toxicity may have contributed to death and secondly to assess whether some patients prescribed PRG are abusing the drug. The cases were identified predominantly from individuals who were prescribed PRG.

2. Methods

2.1. Data collection

The primary data consisted of post-mortem cases with blood samples submitted to the authors' laboratory for toxicology analysis between 2012 and 2014. PRG is not routinely tested for at the laboratory; therefore, analysis was only conducted in cases where possible ingestion of this drug was suspected (from the background information). The laboratory data contained analytical results for PRG, alcohol and other drugs. Information was available regarding the age and gender of the deceased, the circumstances surrounding death and details of prescribed medication. The cause of death was obtained from the respective HM Coroner.

2.2. Blood samples

Only data obtained from post-mortem whole blood was considered in this study. The blood samples were received in a variety of different vials and were frequently unpreserved. Once received at the laboratory, all samples were kept refrigerated (between 2 and 8 °C). Although typically post-mortem blood is taken from the femoral vein, the site of sampling was not specified in some cases.

2.3. Analytical methods

PRG was confirmed and quantified in post-mortem blood by protein precipitation and liquid chromatography mass spectrometry (LC-MS) [18]. The calibration range was from 0.5 to 25 mg/L with a limit of detection of 0.05 mg/L.

Extensive screening of blood and other fluids by LC-MS, gas chromatography-mass spectrometry (GC-MS), and head-space gas-chromatography with flame ionisation detection (GC-FID), was undertaken to determine the presence of other drugs and alcohol.

2.4. Pregabalin concentrations

For the majority of cases, the concentration of PRG was measured accurately. However, in 11 (16%) cases the concentration fell outside the calibration range (less than 0.5 mg/L or greater than 25 mg/L) and an accurate concentration was not obtained. If it was not considered to be crucial to the interpretation of the result, an approximate concentration was quoted. For the purposes of this paper, approximate PRG concentrations have been used where applicable and in the 10 cases that have been documented (Table 1), this is indicated.

3. Results and discussion

3.1. PRG concentrations

PRG blood concentrations were determined in 70 cases over a two year period.

Analysis for PRG was only carried out if its use was suspected, which, in the majority of cases (90%), was due to information provided regarding known prescribed medication. In the remaining cases, most subjects were known to have access to the drug.

PRG post-mortem whole blood concentrations ranged from 0.005 to 226 milligrams per litre (mg/L), with a median of 8.0 mg/L. Of these, 67% had PRG concentrations below or within the reported therapeutic range of 0.4–17 mg/L based on a review of the literature. The cases with therapeutic or sub-therapeutic concentrations had a median PRG level of 3.3 mg/L. The remaining 33% of cases with PRG concentrations greater than 17 mg/L had a median PRG concentration of 32 mg/L (range 18–226).

The data in this study did not present a clear therapeutic range, as a wide range of PRG concentrations were found within subjects prescribed different doses of the drug, thereby making it difficult to distinguish between therapeutic use and abuse. Additionally, the presence of multiple drugs in most cases, did not allow for PRG levels to be directly related to toxicity.

Establishing a therapeutic range from this data was further complicated by the possible influence of post-mortem redistribution on the detected PRG levels. While early studies suggest the impact of post-mortem redistribution may be limited, this study may indicate that a degree of post-mortem may occur. In a significant number of cases in this study where PRG was prescribed the drug was detected at levels above the therapeutic range quoted in the literature for live subjects [15], however they were not significantly elevated and therefore would not be associated with toxicity or fatalities. It should be noted, however, that the suggested therapeutic range is based on plasma levels and the blood to plasma ratio for PRG is not known.

From the information provided in 63 cases, prescriptions for PRG usually ranged from 50 to 600 milligrams daily, which is in accordance with the recommended daily dose, although not all daily doses were provided. Two cases quoted prescribed daily dosages of 900 and 1800 milligrams, which are substantially greater than the recommended dose range. PRG concentrations for these two cases were substantially higher than the top end of the therapeutic range, at approximately 28 mg/L (see Case 6 in Table 1) and 43 mg/L, respectively. These levels could reflect compliance with medication but may have caused some degree of toxicity.

3.2. Prevalence of co-ingested substances

The presence of other drugs seems to be typical of post-mortem cases involving PRG [11]. All cases examined in the present study contained at least one other drug, therefore the concentration above which PRG is likely to cause fatalities cannot be concluded. In several cases (including Case 8, Table 1), pregabalin was likely to be the most significant drug in terms of toxicity, but a contribution from the other drugs detected cannot be ruled out.

It is reported in the literature that PRG use by opioid addicts is relatively commonplace [8], which is supported in this study, with 13% of all showing concurrent use of heroin (measured by the detection of 6-MAM), and a further 28% with morphine present in the absence of 6-MAM. Methadone was detected in 19% of the cases with 20% showing the concurrent use of cocaine. Over 55% of subjects had used diazepam, again supporting other literature reports which note a prevalence of benzodiazepine use in combination with PRG [7,11].

Alcohol was detected at levels consistent with consumption in 24% of all cases in this study. The highest alcohol concentration (135 mg%) was detected in a case where the deceased was found hanged and PRG was detected at a therapeutic concentration. Alcohol was present in 35% of cases with PRG concentrations greater than 17 mg/L.