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Research Article

Gabapentin and Pregabalin Concentrations in Post-Mortem Blood Samples

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Abstract

Introduction: Gabapentin (GBP) and Pregabalin (PRG) are commonly prescribed for the treatment of neuropathic pain, seizures and anxiety disorders. A number of studies have been published which have shown a rise in GBP and PRG prescriptions and an increase in misuse of these medication. As well has this, it has been shown that GBP is often co-ingested with other medications such as ethanol and benzodiazepines. Although the reason for misuse of these drugs is unclear possible motivations include recreational use, intentional self-harm and controlling pain. The aim of this study is to report GBP, PRG and co-administered drug concentrations in post-mortem blood received by Leicester Royal Infirmary during 2016.

Methods and Materials: All relevant post-mortem toxicology reports received by the Leicester Royal Infirmary (LRI) in 2016 were identified using the keyword 'gabapentin' and 'pregabalin'. The reports contained information about the decedent's age, date of death, date of sample and post-mortem GBP and/or PRG and co-administered drug concentrations measures from blood samples from the femoral vein. Analysis included age, gender and concentrations of GBP/PRG and co-administered drugs.

Results: The search identified 350 post-mortem toxicology reports which consisted the keyword 'gabapentin' and/or 'pregabalin' received by the Leicester Royal Infirmary during the year 2016. Of these 268 (76.57%) reports showed detectable concentrations of GBP and/or PRG in post-mortem blood and met the criteria for analysis listed above. Their age ranged from 18 years to 83 years, and the median age overall was 44 years. The PRG concentration ranged from 0.011 mg/l to 367 mg/l. The GBP concentrations ranged from 0.49 mg/l to 434 mg/l. The most commonly co-administered groups of drugs were: opioids, benzodiazepines, alcohol and antidepressants.

Discussion: This report reinforces the findings of numerous studies that GBP and PRG are commonly used drug. Given that there is strong evidence to suggest that there is an increase in prescriptions issued for gabapentinoids alongside evidence it is important for prescribers constantly review the medication for decedents on these medications and be on the lookout for signs of abuse and misuse.

Keywords: *Gabapentin (GBP); Pregabalin (PRG)*

Introduction

Gabapentinoids consist of gabapentin (GBP) and Pregabalin (PRG) are commonly prescribed medication. GBP can be used for treatment of focal seizures and neuropathic pain, for which it is licensed in the UK. In addition to these PRG is licensed for generalised anxiety disorder. As well as this, gabapentinoids are used off license for migraine prophylaxis, psychiatric disorders, painful diabetic neuropathy and substance misuse disorders [1-3].

Gabapentinoids work in a similar manner, although the exact mechanism of action for them has not been defined. It is thought that it has a high affinity to α2δ subunit of voltage-dependent calcium channels in presynaptic neurones, thereby decreasing the influx of calcium into the cell [4]. This in turn reduces the release of excitatory neurotransmitter which causes nociception and in some people epileptic seizures.

With regards to protein binding, mode of excretion via the kidneys and minimal drug-drug interactions gabapentin and pregabalin have comparable properties, however they have very different bioavailability. Gabapentin's oral bioavailability ranges from 27% to 60% depending on the dose administered and its absorption is variable from person to person [5,6]. On the other hand, pregabalin has a linear absorption and more predictable bioavailability averaging about 90% [6].

The usual dose of GBP varies depending on the condition it is being used to treat. For seizures and neuropathic pain in adults the maximum amount which can be prescribed is 3.6g daily divided into 1-3 doses. For migraine prophylaxis for adults the maximum amount which can be prescribed is 2.4g daily in divided doses. Therapeutic range of gabapentin in plain blood ranges from 2 - 20 mg/l [7]. The recommended dose of PRG also varies depending on its indication, but a maximum of 600mg can be given daily divided in 2 - 3 doses. The peripheral blood therapeutic range for PRG is between 0.4 mg/l - 17 mg/l [8].

Absorption	Ranges from 60% - 27%
Protein binding	< 3% circulates bound to plasma protein
Metabolism	Minimal
Route of Elimination	Renal
Half-life	4.8-8.7 hours
Volume of distribution	0.6 - 0.7 $l.kg^{-1}$

Table 1: *Gabapentin pharmacology [5].*

Absorption	Bioavailability: > 90%
Protein binding	Does not bind to plasma proteins
Metabolism	Minimal
Route of Elimination	Renal
Half-life	6.3 hours
Volume of distribution	Apparent: 0.5 $l.kg^{-1}$

Table 2: *Pregabalin pharmacology [1,3,6,9].*

There has been mounting evidence to suggest that there has been an increase in prescribing of gabapentinoids in the UK. Over 5 years it has been shown that pregabalin prescriptions increased by 350% and gabapentin prescriptions increased by 150%. In conjunction with this concerns have been raised about abuse of gabapentinoids and there is evidence to validate this. These drugs are being detected in post-mortem toxicology reports [10].

Materials and Methods

In order to identify the relevant post-mortem toxicology reports, the keyword 'gabapentin' and 'pregabalin' was used. All the reports had been received by the laboratory at the Leicester Royal Infirmary (LRI). The reports contained information about the decedent's age, date of death, date of sample and post-mortem GBP, PRG and co-administered drug concentrations measures from blood samples from

the femoral vein. Analysis included age, gender and concentrations of GBP and/or PRG and co-administered drugs. Analysis excluded decedents younger than 18 years of age and decedents for whom an age could not be calculated. Circumstances surrounding the death were also not considered as there was limited reporting of clinical histories in some cases.

Results

Demographics

The search identified 350 post-mortem toxicology reports which consisted the keyword 'gabapentin' and/or 'pregabalin' received by the Leicester Royal Infirmary during the year 2016. Of these 268 (76.57%) reports showed detectable concentrations of GBP and/or PRG in post-mortem blood and met the criteria for analysis listed above. 10/268 (0.037%) had both PRG and GBP detected. 149/268 (55.76%) had only PRG detected. 109/268 (40.52%) had only GBP detected.

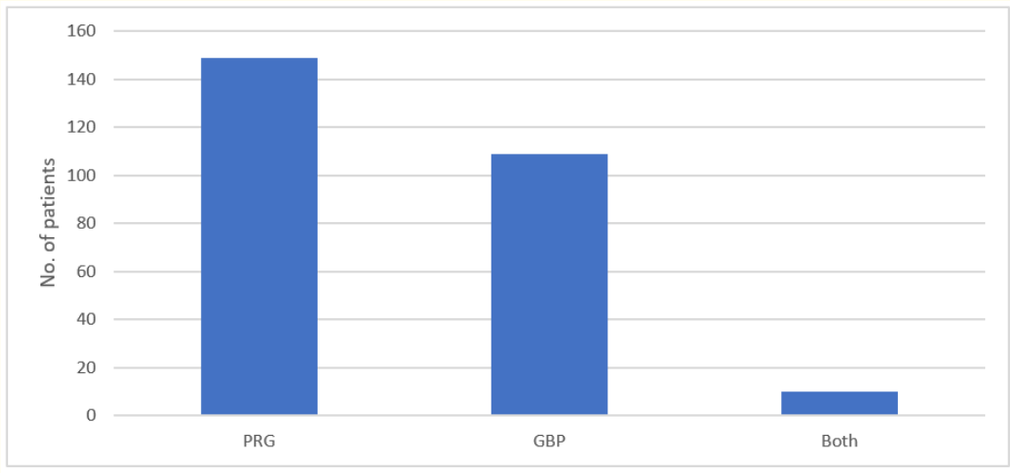

Figure 1: *Graph illustrating.*

Although the rest of the 82 (23.43%) reports did contain GBP and/or PRG in the clinical history of the decedent or in the circumstances around death, there was none detected in the toxicology screen or the decedents did not match the criteria listed above.

In almost all of the age ranges there were more male decedents than female decedents. Amongst the 268 reports in which PRG/GBP was detected 169/268 (63.06%) decedents were male, and 99/268 (36.94%) decedents were female. Their age ranged from 18 years to 83 years, and the median age overall was 44 years. But the median age for GBP users was 48 years whereas the average age for PRG users was 42 years.

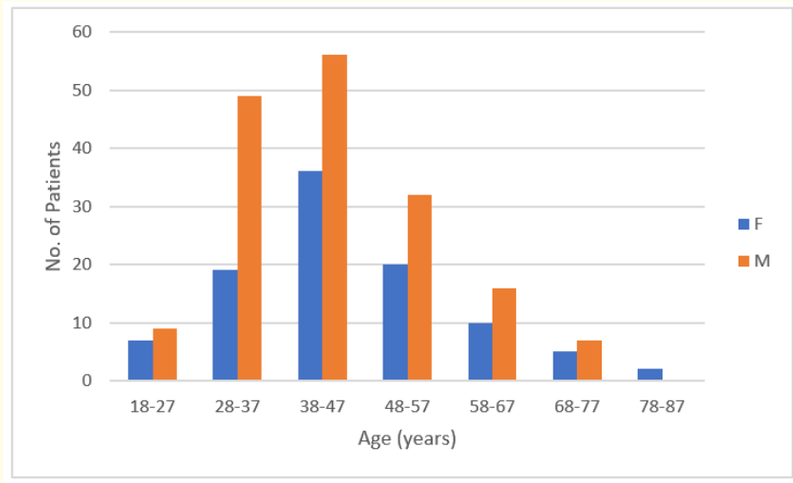

Figure 2: *Graph showing the combined age and gender distribution for patients who had GBP and/or PRG detected in their toxicology report. The median age overall was 44 years.*

PRG concentrations

In the 159 reports analysed the PRG concentration ranged from 0.011 mg/l to 367 mg/l. From the reports analysed 111/159 (69.81%) where within the therapeutic range (0.4 mg/l - 17 mg/l) [8]. 2/159 (1.26%) were below the therapeutic range (< 0.4 mg/l) and 46/159 (28.93%) were above the therapeutic range (> 17 mg/l).

The age range, for the decedents who had a PRG levels above the therapeutic range, was 21-60 years with majority of decedent, 20/46, were in the 31 - 40 age range (Figure 3). Of the 46 decedents in whom the PRG levels were above the therapeutic range 11/46 were female and 35/46 were male.

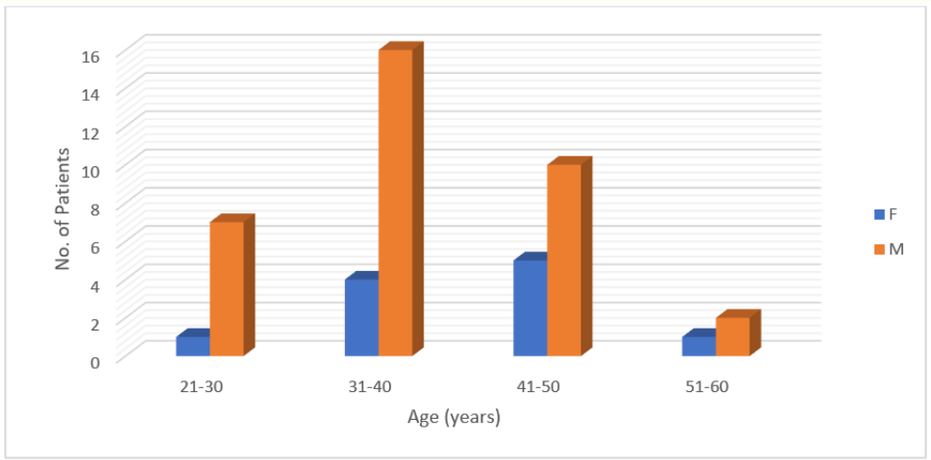

Figure 3: *This graph shows the age distribution of decedents in whom the PRG level was above the therapeutic range. Overall there were 46/268 decedents in whom the PRG detect was above the therapeutic range. The majority of decedent, 20/46, were in the 31 - 40 age range.*

GBP concentrations

In the 119 reports that were analysed the GBP concentrations ranged from 0.49 mg/l to 434 mg/l. The median concentration for all 119 decedents was 26.6 mg/l. From the reports analysed 68/119 (57.14%) were within the therapeutic range (2 mg/l - 20 mg/l) [7]. 7/119 (5.88%) were below the therapeutic range (< 2 mg/l) and 44/119 (36.97%) were above the therapeutic range (> 20 mg/l). The age range, for decedents who had a GBP level above the therapeutic range, was 24-83 years, with the majority of the decedents falling in the 44 - 53 and 54 - 63 age ranges (Figure 4). Of the 44 decedents in whom the GBP levels were above the therapeutic range 18/69 were female and 26/69 were male.

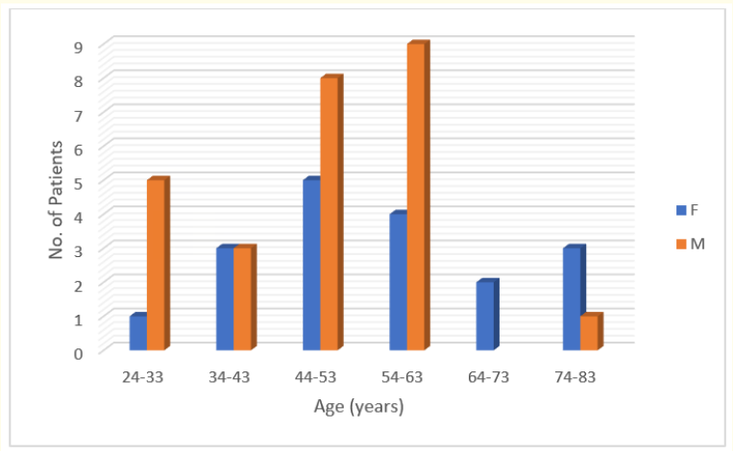

Figure 4: *This graph shows the age distribution of decedents in whom the GBP level was above the therapeutic range. Overall there were 44/268 decedents in whom the PRG detect was above the therapeutic range.*

Post-mortem interval between DOD and DOS

For 16/268 of the decedents it was not possible to calculate the time from date of death (DOD) to date of sample (DOS) as information regarding DOD was not available - hence these were taken out when analysing the data. For the 252 reports that were analysed the post mortem interval (the number of days between death and blood sampling) ranged from 0 days to 19 days with the mean post mortem interval being 4.09 days.

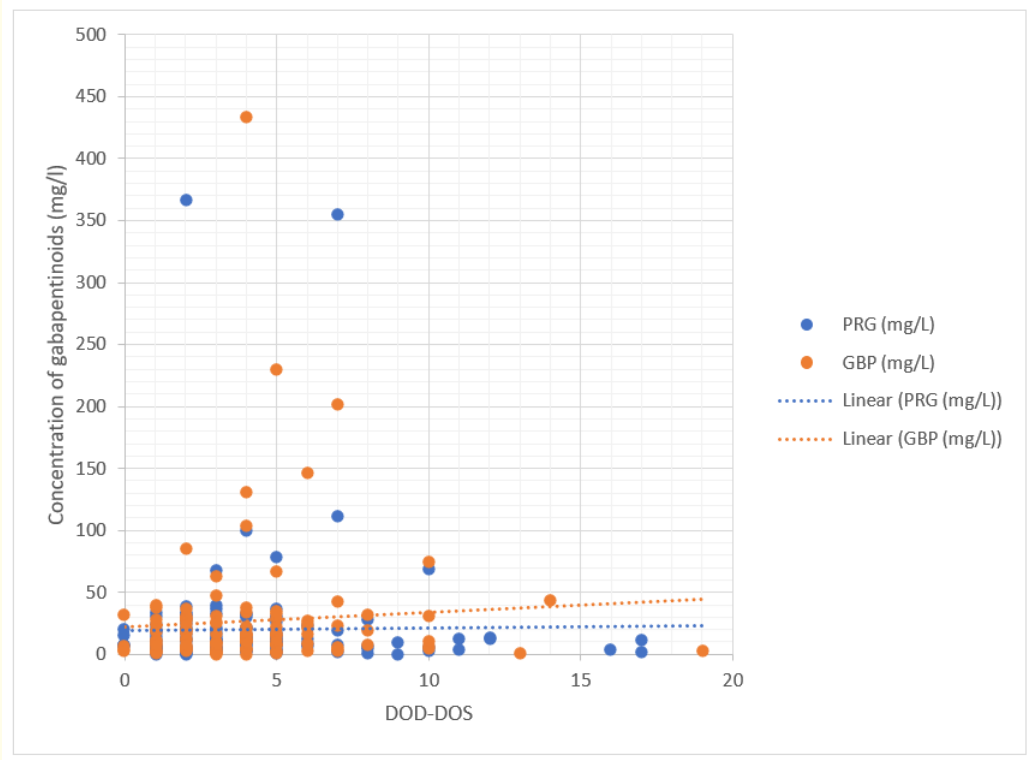

Figure 5: *Graph showing GBP and PRG concentration against Post Mortem interval. The post-mortem interval ranges from 0 days to 19 days. The trend line (orange - GBP and Blue- PRG) shows a weak relationship between the GBP concentration and the post-mortem interval, but the line does not show a relationship between PRG concentration and post mortem interval.*

Co-administered drugs

Analysis of the data identified 264/268 reports in which other drugs were co-administered with gabapentinoids. In the remaining 4/268 no other drugs apart from gabapentinoids was detected. The most commonly co-administered groups of drugs were: opioids- with at least one opioid detected in 227/268 (84.70%) decedents, benzodiazepines- with at least one benzodiazepine detected in 137/268 (51.12%) decedents, alcohol- with it being detected in 88/258 (32.84%) decedents and antidepressants- with at least one antidepressant being detected in 69/268 (25.75%) decedent (Figure 6).

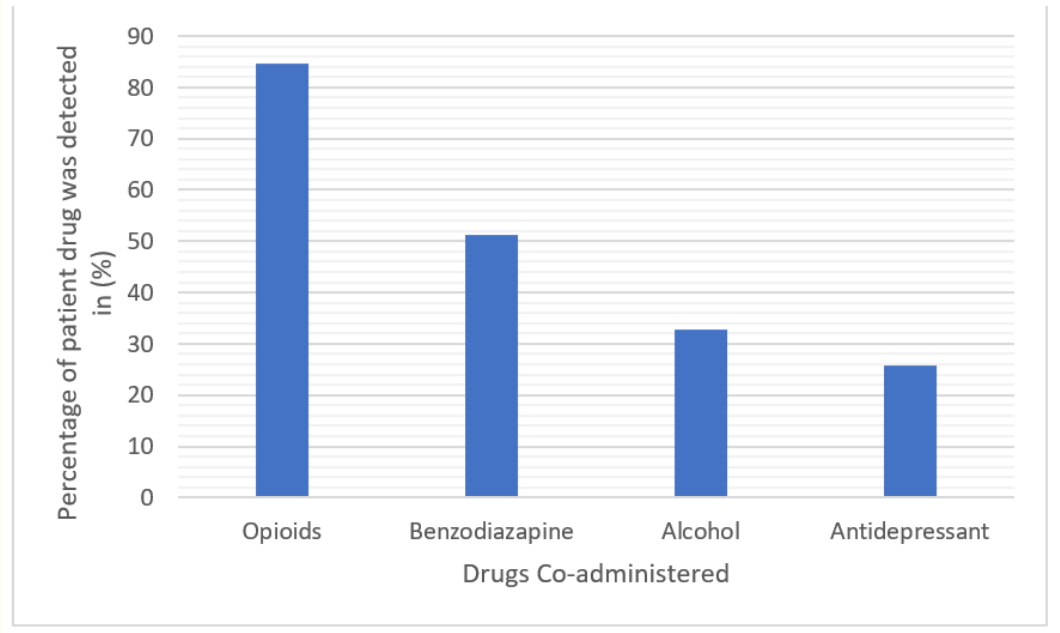

Figure 6: *Post-Mortem blood concentration of common drugs co-administered with gabapentinoids.*

On further analysis of the post mortem reports where at least one opioid was detected, 147/268 had morphine co-administered. Other commonly co-administered opiates included codeine, EDDP, Methadone and Tramadol (Figure 7). Similarly, on analysis of post mortem reports where at least one antidepressant was detected, 71/268 had nortriptyline co-administered. The other commonly co-administered antidepressants included Mirtazapine, Amitriptyline, Fluoxetine and Norfluoxetine.

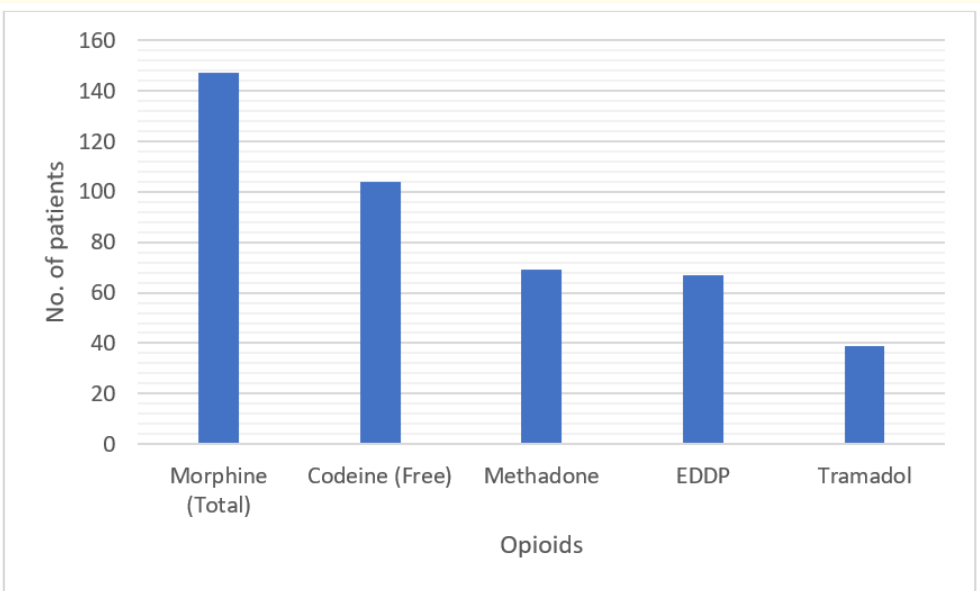

Figure 7: *Post-mortem blood concentrations of common opioids co-administered with gabapentinoids.*

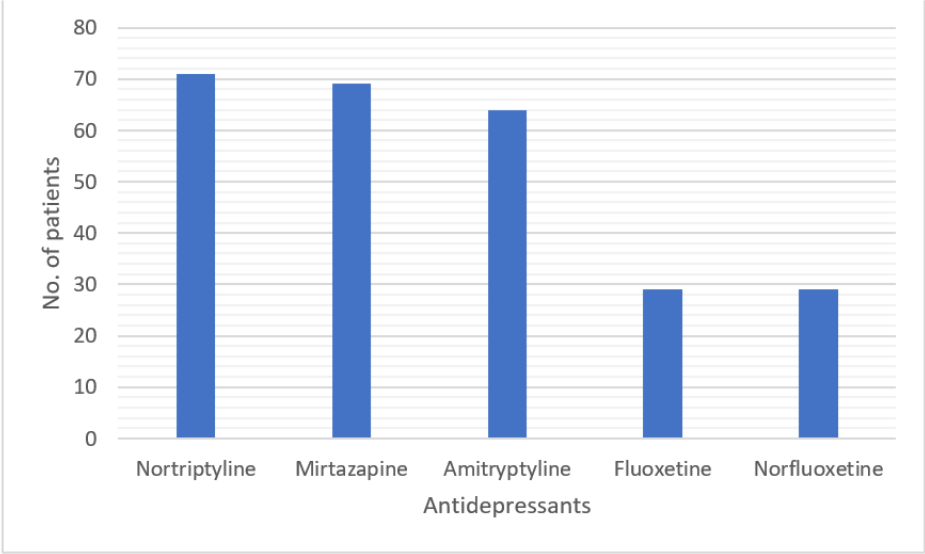

Figure 8: *Post-mortem blood concentrations of common antidepressants co-administered with gabapentinoids.*

Discussion

Demographics

Of the 268 reports in which PRG/GBP was detected 169/268 decedents were male, and 99/268 (36%) decedents were female. Their age ranged from 18 years to 83 years, and the median age overall was 44 years. But the median age for GBP users was 48 years whereas the average age for PRG users was 42 years. One study reported that for decedents with GBP abuse the median age was 30 years and the median age for GBP users was 58 years [11]. Another study which looked at people presenting to hospital with gabapentinoid over dose reported a median age of 37 years [12]. However, in only 94/268 and 69/268 decedents had PRG and GBP concentrations respectively above the therapeutic range, 17 mg/l and 10 mg/l respectively. Although most of the decedents in who the drug ranges were over the therapeutic range were male- this is not necessarily a significant finding as overall there were more male decedents than female. The majority of the decedents (19/69), in whom the GBP levels exceeded 10 mg/l, were in the 44 - 53 age range, whereas, for PRG the majority of decedent (20/46), in whom PRG levels exceed 17 mg/l, were in the 31 - 40 age range. But we cannot make any conclusive remarks on the age and gender distribution with regards to gabapentin abuse as the histories provided with each decedent does not allow us to differentiate between users and misusers or decedent who took an accidental or intentional overdose.

GBP/PRG concentrations and co-administered drugs

The literature suggests that the peripheral serum therapeutic range for GBP is between 2 mg/l - 20 mg/l and the peripheral serum therapeutic range for PRG is between 0.4 mg/l - 17 mg/l. [7,8]. There is not expected to be a significant difference between whole blood and serum concentrations. With regards to GBP 68/119 whole blood concentrations were within the therapeutic range (2 mg/l - 20 mg/l) [7]. 7/119 where below the therapeutic range (< 2 mg/l) and 44/119 were above the therapeutic range (> 20 mg/l). With regards to PRG 111/159 were within the therapeutic range (0.4 mg/l - 17 mg/l) [8], 2/159 were below the therapeutic range (< 0.4 mg/l) and 46/159 were above the therapeutic range (> 17 mg/l).

In the study, there is been a time difference of a number of days between the date of death, date of sample collection. This can potentially have an impact of the results we received for the levels of gabapentin in their blood due to post-mortem redistribution (PMR). Although

the data showed that there is a relationship between GBP concentrations and post-mortem interval, to reach a conclusion we would need to analyse the ante-mortem drug concentrations. But there would be no way to access these. There has been a limited number of studies which have looked at the post-mortem redistribution of gabapentin. One study investigated the PMR of gabapentin in 30 cases. They also had one participant for whom they had ante-mortem and post-mortem gabapentin concentrations, which showed that gabapentin levels were not altered, but this was a singular observation. The study concluded that gabapentin does not undergo PMR however the study included a small number of participant [13]. Similarly, we have limited information on PRG with regards to PMR, however some studies have suggested researched this [14].

Analysis of the data identified 264/268 (98.51%) reports in which other drugs were co-administered with gabapentinoids. In the remaining 4/268 (1.46%) no other drugs apart from gabapentinoids was detected. The most commonly co-administered groups of drugs were: opioids, benzodiazepines, alcohol and antidepressants. At least one opioid was detected in 227/268 (84.70%) decedents. IN another study it was found that there were no post-mortem cases that did not have co-administered drugs alongside PRG and GBP. In their study they found that 91.4% of the PRG and 87.5% of the GBP abuse cases opioids were also present. In reports where opioids were not detected other drugs such as benzodiazepines were detected- this was another common drug seen in this study [11]. A systematic review also found that three toxicology studies showed that gabapentin abuse also involved the use of alcohol, opioids, antidepressants and other CNS depressants. Another study which looked at gabapentinoid abuse by using questionnaire in substance misuse clinics. This showed that 38% of people who self-reported as gabapentinoid abusers, did so to potentiate 'high' from methadone [15]. Studies have shown that gabapentinoid abuse tends to commoner amongst opioid users- one reason for this may be because decedent experiencing pain often gets both medications co-prescribed [16].

Several studies looked at the motivation behind gabapentinoid use. The motivations highlighted include: easing pain, achieve euphoric highs, control withdrawal symptoms from other medication, potentiate effects of other drugs and improved sleep [3,16,17]. One study described that 38% of a substance misuse sampled in their study took GBP/PRG in combination with methadone to potentiate the effects of methadone [15]. An internet based survey reported that the lifetime prevalence of GBP misuse in the UK was 1.1% and 0.5% for PRG [18]. Over the period of 2011-2013 through electronic prescribing data it has been shown that there has been an increase in the prescribing of gabapentin by 46% and prescribing of pregabalin is increased by 53% [2]. Acquiring gabapentinoids from health services is only one of the ways on which people are able to acquire GBP other methods include from close acquaintances, internet, buying from abroad [19].

Limitations and Future Direction

This study reported the GBP and PRG concentrations in post-mortem blood samples in 268 decedents, received by the Leicester Royal Infirmary in 2016. The study showed that the gabapentin and pregabalin concentrations ranged in the decedents with some reports showing co-administration of other drugs such as opioids. Many reports discussed above have suggested that there has been in an increase in the number of decedents who are able to acquire gabapentinoids through health services- without accounting for changes in the number of people who acquire it by a different method such as the internet. In this study we were unable to conclusively say whether or not a decedent died from a gabapentin overdose due to the limited information on the history and circumstances around death for some decedents. Another aspect which needs to be considered if how plasma concentration of the drug changes post-mortem for which we would ideal need ant-partem toxicology reports.

Conclusion

This report reinforces the findings of numerous studies that GBP and PRG are commonly used drugs. As well as this, it adds to already prominent evidence that gabapentinoids are abused alongside other medication such as opioids and benzodiazepines. Given that there is strong evidence to suggest that there is an increase in prescriptions issued for gabapentinoids alongside evidence which suggest misuse is common it is important for prescribers to consider the necessity of prescribing these drugs. They must also, constantly review the medication for decedents on these medications and be on the lookout for signs of abuse and misuse.

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