

Abuse of pregabalin – results of the postmortem toxicology from 2010 to 2012

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Abstract

Aims: Pregabalin is a prescription drug for the treatment of neuropathic pain, partial epilepsy and generalized anxiety disorder. In the last years, a misuse of pregabalin has been reported in Germany. In the USA, pregabalin is listed as a substance with potential abuse.

In order to monitor a potentially increasing abuse of pregabalin, it was decided to analyze routinely for pregabalin in postmortem toxicology.

Methods: Femoral blood was used for toxicological analysis. In two cases femoral blood could not be collected and heart blood was analyzed instead. After protein precipitation with acetonitrile, the supernatant was processed and then analyzed with LC-MS/MS at the FTC.

Results and Discussion: Pregabalin was detected in 43 of 982 cases (4.4%) within two years. The concentration range was between 0.04 mg/L and 23.8 mg/L. The median of the concentration of pregabalin was 5.18 mg/L. Illicit and licit drugs, mostly opiates/opioids, benzodiazepines and antidepressants, were additionally detected in each case. In the first year, pregabalin was found in 10 of 489 cases (2.0%). In the second year, the number of cases with pregabalin increased to 33 of 493 cases (6.7%). In the subgroup of drug-dependant individuals the percentage was 5.5% (4 of 72 cases) in the first year and 29.8% (26 of 87 cases) in the second year.

Conclusion: There is an abuse of pregabalin especially by drug-dependant individuals. An increasing abuse of pregabalin is to be expected for the next years.

1. Introduction

Pregabalin, a gamma-aminobutyric acid analogue, is a prescription drug sold under the trade name Lyrica[®] for the treatment of neuropathic pain, partial epilepsy and generalized anxiety disorder. In the last years, a misuse of pregabalin has been reported in Germany [1,2] as well as in other countries like Sweden [3]. An increasing tolerance of persons taking pregabalin and even dependence and withdrawal symptoms after discontinuation are described too [1-3]. In the USA, pregabalin is listed as a substance with potential abuse [4]. In order to monitor a potentially increasing abuse of pregabalin, it was decided to analyze routinely for pregabalin in postmortem toxicology at the institute of forensic medicine in Munich.

2. Material and Methods

The blood samples were obtained from the autopsy. Peripheral (femoral) blood was used for toxicological analysis of postmortem cases. In two cases femoral blood could not be collected and heart blood was analyzed instead.

For protein precipitation, 100 µL of blood were treated with acetonitrile. The supernatant was vaporized to dryness under nitrogen and reconstituted in buffer. A mixture of internal stan-

dards was added before preparation. For pregabalin, the used internal standard was methamphetamine-*d14* (m/z 164→130). The extracts were analyzed by an LC-MS/MS (ABSciex API 4000) with electrospray ionization operated in positive mode at the FTC. Separation was achieved on a Zorbax Eclipse XDB-C8 column (4.6 x 150 mm) by Agilent. The mobile phase consisted of solvent A (5 mM ammonium formate and 0.1% formic acid in water) and solvent B (5 mM ammonium formate and 0.01% formic acid in methanol). Two transitions were set up, one for the quantification of pregabalin (m/z 160→55) and one as the qualifier of pregabalin (m/z 160→83). Analyst Software was used for identification and quantification.

3. Results and Discussion

More than 4200 autopsies and thereof 982 toxicological analyses were performed within two years (October 2010 – September 2012). Pregabalin was detected in 4.4% ($n=43$). The median of the pregabalin concentration in whole blood was 5.18 mg/L (range 0.04 – 23.8 mg/L) and therefore at the upper limit of the reported therapeutic concentration (2 – 5 mg/L) in plasma [5]. There are no data about the blood/plasma ratio of pregabalin [6]. One or more other licit or illicit drugs, mostly opiates/opioids, benzodiazepines and antidepressants, were additionally detected in every case. In the first year, pregabalin was found in 2.0% of the analyzed cases (10 of 489 cases). In the second year, the number of cases with pregabalin increased to 6.7% (33 of 493 cases). The age of the deceased was between 24 and 93 years.

Due to information of police, family members and the situation at the scene, 159 of 982 cases could be attributed to the group of drug-dependant individuals, most of them (93.7%) were opiate/opioid dependant. In this subgroup pregabalin could be detected in 18.8% (30 of 159 cases) and thus at a much higher percentage: from 5.5% (4 of 72 cases) in the first year to 29.8% (26 of 87 cases) in the second year. Our analysis revealed a median age of 34 years (range 24 and 47) and a preponderance of the male gender (73.3%, $n=22$).

In one case heart blood was analyzed resulting in the highest detected pregabalin concentration of 23.8 mg/L. To our knowledge there are no data about postmortem redistribution of pregabalin in heart blood. This high concentration could be an indication of a postmortem redistribution into heart blood, hence this pregabalin concentration was omitted. As a result of this, the median of the pregabalin concentration in the group of drug-dependant individuals was 5.73 mg/L (range 0.17 – 19.5 mg/L).

More than 0.30‰ (0.38 – 1.98‰) blood alcohol was found in 30% (9 of 30 cases). Besides pregabalin, 61 additional substances were detected by toxicological analysis. The frequency of the detected groups of substances, including alcohol, is described in figure 1. Opiates/Opioids were found in every case. In 76.6%, benzodiazepines were consumed additionally to pregabalin, headed by diazepam and followed by lorazepam and bromazepam. Further additional drug intakes were neuroleptics (33.3%) and antidepressants (26.6%). In figure 2 the frequency of the detected opiates/opioids is shown in more detail. Fentanyl and methadone are the most found opioids followed by heroine.

4. Conclusion

There is an (ab)use of pregabalin especially in the group of opiate/opioid-dependant individuals. An increasing abuse of pregabalin is to be expected for the next years. Regarding to the fact, that pregabalin is investigated amongst others for the treatment of benzodiazepine dependence, physicians should be aware of potential abuse of pregabalin and prescribe pregabalin with utmost caution.

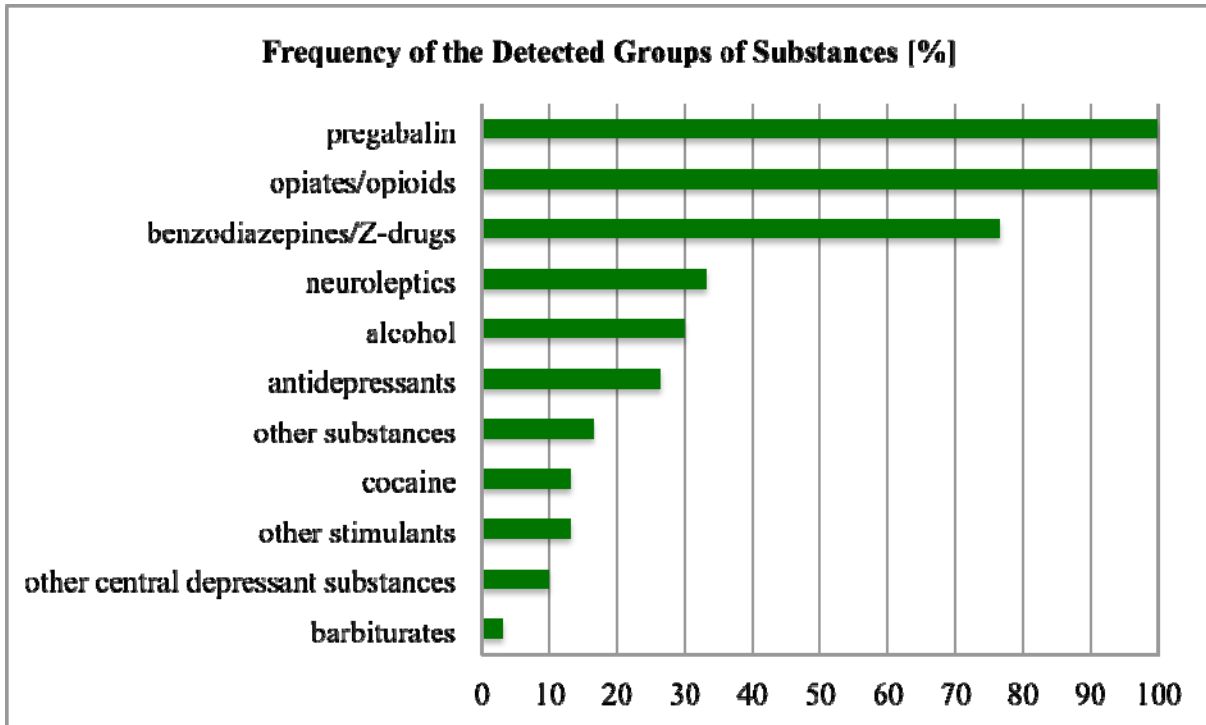


Fig. 1. Frequency of the detected groups of substances in the group of pregabalin positive drug-dependant individuals.

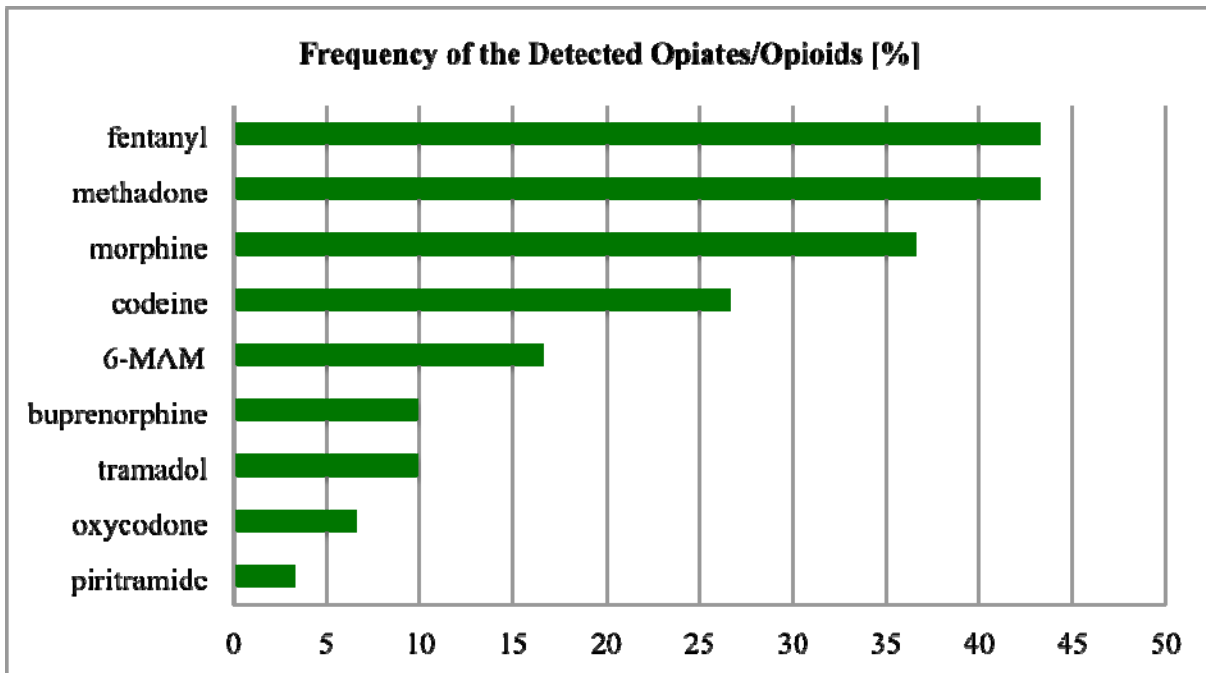


Fig. 2. Frequency of the detected opiates/opioids in the group of pregabalin positive drug-dependant individuals.

5. References

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