

Assessment of the Use of Point-Of-Care Pregabalin Testing For Drug Monitoring, Compared to Gas Chromatography Mass-Spectrometry – A Pilot Study

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Abstract

Pregabalin is a structural derivative of the inhibitory neurotransmitter Gamma-aminobutyric Acid (GABA) and is used in the treatment of anxiety disorder, neuropathic pain and as an anti-convulsant. The prescription of pregabalin has increased in recent years along with reports of its abuse (especially through taking high doses). Consequently, there is a need to monitor the use of pregabalin in patients prescribed the drug as well as those potentially using it without prescription. Point-of-care testing has been used for many years in monitoring illicit drug use but has only become available recently for pregabalin. In order to validate the effectiveness of this approach, a point-of-care testing device for pregabalin was compared with 'gold standard' gas chromatography with mass-spectrometry. The results of a pilot study involving 300 patient urine samples showed that the point-of-care pregabalin testing device was appropriate for determining instances where pregabalin had not been used, but due to the observation of 4% false positives, mass-spectrometry confirmation is recommended (as is usually the case for immunoassay-based approaches, especially in a medico-legal context).

Keywords: Pregabalin; Point-Of-Care Testing; GC-MS; Neuropathy

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How this fits in with quality in primary care

What do we know?-the use and abuse of pregabalin has increased in recent years; requiring monitoring of patients prescribed the drug as well as identifying potential abusers.

What does this paper add?-this paper demonstrates that point-of-care testing for pregabalin is a viable option for patient monitoring for pregabalin use. The authors believe this to be the first published data concerning pregabalin point-of-care testing especially in comparison with 'gold standard' mass-spectrometry confirmation.

Introduction

Pregabalin is an anticonvulsant drug (anti-epileptic) prescribed for the prevention and reduction of epileptic seizures as well as in anxiety and pain management where it is also used to treat fibromyalgia and pain caused by nerve damage as in diabetic neuropathy; spinal cord injury and post-herpetic neuralgia (herpes

zoster) [1]. Pregabalin slows down the impulses in the brain and influences the nervous system by affecting the messengers that transfer pain signals. Whilst pregabalin is a structural derivative of the inhibitory neurotransmitter Gamma-aminobutyric Acid (GABA); its exact mechanism is not completely understood.

In recent years; reports have been emerging of pregabalin being abused at high doses (e.g. between 600-5000 mg) to produce feelings of relaxation; calmness and euphoria (this includes enhancing the euphoric effects of opiates). Along with its availability through online black market pharmacies; pregabalin

has been encountered in individuals not prescribed the drug [2,3]. This includes instances of intoxication (including driving under the influence of drugs) and some deaths [4-9].

Against this background; particularly with the increasing burden of pregabalin use and reports of its abuse; there has been an increasing requirement to monitor pregabalin use through detection in biological fluid; especially urine. Due to the nature of pregabalin; it often requires specific extraction from the matrix and analysis through chromatographic techniques (e.g. Liquid Chromatography with Mass-Spectrometry (LC-MS) or Gas Chromatography with Mass-Spectrometry (GC-MS)) [9]. Whilst the use of micro-extraction and analysis of dried blood spots has improved the efficiency and automation of analysis; the use of these techniques have financial and resource implications that require active laboratory involvement [10]. Consequently; as for some other drugs; Point-of-Care-Testing (POCT) devices have been used for many years to allow ready testing of patient urine samples to assist with drug monitoring. Recently; an immunoassay-based system for the POCT of pregabalin in urine has become available consisting of a POCT cup with multi-drug analysis and specific pregabalin analysis. It was therefore important to validate the sensitivity and selectivity of the pregabalin POCT cups to explore their reliability against standard chromatographic confirmatory platforms. A pilot study was undertaken to determine the detectability of pregabalin using a POCT cup against a qualitative GC-MS method towards establishing the clinical reliability of the POCT product. The study involved analysis of patient urine samples by POCT along with GC-MS; with a comparison of findings.

Methodology

POCT cups for pregabalin screening in urine were purchased from Matrix Diagnostics (London; UK) and included both a multi-parameter Unknown Drug Screening (UDS) cup and a cassette with an associated stated detection limit for pregabalin of 500 mg/mL in urine. To determine any interference of other drugs; drug screening was undertaken using two different laboratory methods involving an initial screening method followed by a confirmatory method using different chemical and physical principles. Screening for drugs of abuse was performed using the Multigent homogeneous enzyme immunoassay (Abbott; USA) using ready-to-use liquid reagents. The assay uses monoclonal antibodies that detect illicit drugs in urine. It is based on the competition between an enzyme labeled drug and the drug from the urine for a fixed number of specific antibody binding sites. In the absence of drug from the sample; the specific antibody binds to the drug labeled with Glucose-6-Phosphate Dehydrogenase (G6PDH) and the enzyme activity is inhibited. This reaction creates a direct relationship between the drug presence and concentration in the urine and the enzyme activity. Confirmation of any drugs presumptively identified was undertaken using a Shimadzu Ultra-2010 GC-MS system (Shimadzu; Japan). The GC-MS confirmatory procedure uses full scan product ion spectra to identify drugs that are present; including pregabalin.

Over a one month period on multiple days; the urine from

Table 1 Comparison of immunoassay and GC-MS results for pregabalin in 300 patient urine samples.

n=300	GC-MS Positive	GC-MS Negative
Immunoassay Positive	46	9
Immunoassay Negative	0	245

300 patients was collected directly into the POCT cups and the presumptive result for pregabalin recorded. Each sample was then re-analysed by qualitative GC-MS without knowledge of the presumptive result.

Results and Discussion

Out of the 300 patient urine specimens; pregabalin was detected by both immunoassay and specific GC-MS in 46 samples; with no pregabalin being detected in 245 samples (by either technique) (Table 1). As such the analytical result for pregabalin was identical in 97% (291) instances. Of the remaining 9 results; the findings indicated a false positive result for the POCT where pregabalin was presumptively detected by immunoassay but was not detected by GC-MS; indicating a false positive rate of 4% within the cohort. False positives typically occur when the drug in question shares some common structural similarities with a different drug that is present in the sample. As previously mentioned; whilst pregabalin shares some structural similarity with GABA; the ubiquity of this neurotransmitter would not be a likely explanation of this result. Pregabalin also shares some similar structural similarity to another anti-convulsant; gabapentin but due to a difference in chemical configuration this should also not necessarily be the reason. As pregabalin has a relatively simple chemical structure with various common chemical moieties (e.g. amine group and carboxylic acid group within a carbon chain) this presents difficulties in developing highly specific antibodies to this drug. As such there may be some structurally related endogenous compounds derived from some food stuffs as well as other medicines or their metabolites that may account for the few false positive results observed. However; as there was no obvious analytical reason for this based on the wider drug screening performed; the possibility of false positives require additional investigation but represented only a 4% rate of occurrence. As there were no false negative results; this indicates that the POCT product could be used to exclude negative specimens and pre-select presumptive pregabalin positive specimens for GC-MS confirmation. This is the current case with drugs of abuse testing for common drugs such as morphine; cocaine; amphetamine; etc. The use of a POCT approach for pregabalin will therefore increase efficiency and productivity for pregabalin testing and patient monitoring which will assist clinicians. The use of pregabalin immunoassay may also be of relevance for laboratories that undertake high throughput urinary testing for other clinical as well as potentially medico-legal and forensic purposes but would require specific LC-MS or GC-MS confirmation of any positive finding—as is also currently the case for immunoassay drug testing in forensic toxicology.

Conclusion

The result of this pilot comparison study showed a reliability rate of 97% for the patient cohort tested when using the POCT

cup for presumptive pregabalin detection. This approach could be quickly incorporated with the clinical assessment and initial diagnosis of a physician to assist in an effective clinical decision making process as well as being considered for other toxicological applications. However; the possibility of obtaining a false positive result was observed in 4% of the confirmed negative samples. As such; use of or access to a LC-MS or GC-MS confirmatory method should also be involved.

Furthermore; to provide increased reliability and confidence; it is recommended that a larger number of specimens 1000 or more

be analysed and results assessed. This is especially important given potential drug interferences with POCT assays including other prescription drugs; over-the-counter medicines and possible dietary substances.

Declaration

The authors declare that appropriate patient consent has been obtained and that all reasonable steps have been taken to maintain patient confidentiality. Furthermore there are no sources of funding or conflicts of interest to disclose.

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