Gabapentin and pregabalin are well established for the treatment of seizures and neuropathic pain. Both drugs are eliminated primarily unchanged by renal excretion. As part of an ongoing research program to improve and expand drug testing methods for compliance monitoring of pain patients, the prevalence and concentrations of gabapentin and pregabalin in urine specimens from chronic pain patients were determined by a validated liquid chromatography–tandem mass spectrometry assay. The study was approved by an Institutional Review Board. A total of 57,542 urine specimens from 231 pain clinics located in 19 states were analyzed over the period of November 24, 2009, through May 2010. The limit of quantitation (LOQ) and upper LOQ of the assays for both drugs were 2.5 and 1000 µg/mL, respectively. Gabapentin was identified in 7013 specimens (12.2% prevalence), and pregabalin was identified in 4799 patients (8.3% prevalence). Generally, gabapentin concentrations were more than twofold higher than pregabalin, consistent with their relative potencies. Interestingly, both drugs were found in specimens from 249 patients, likely representing switching of prescriptions by the prescriber.

Introduction

Gabapentin (Neurontin®) and pregabalin (Lyrica®) are anticonvulsant drugs used for the treatment of neuropathic pain and partial seizures. Both drugs have been recommended as first-line pharmacologic treatment for neuropathic pain (1–3). Pain management practitioners rely on drug testing for gabapentin and pregabalin as part of an assessment of patient compliance, particularly because these agents are often used in combination with opioid therapy (1–4). Although the abuse potential of gabapentin and pregabalin is considerably lower than that of opioids, there have been published case reports of gabapentin and pregabalin abuse and dependence (5,6).

In the United States, gabapentin is available by prescription only and pregabalin is a Schedule V controlled substance. As illustrated in Figure 1, both compounds are structural analogs of the neurotransmitter gamma-aminobutyric acid (GABA), but neither binds to GABA receptors. Like gabapentin, pregabalin binds to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues, reducing depolarization-induced calcium influx and, thereby reducing release of excitatory neurotransmitters such as glutamate, noradrenaline, and substance P (7). These actions are thought to be responsible for their antinociceptive and antiseizure effects. The most common adverse reactions of gabapentin and pregabalin are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and difficulty with concentration/attention (7,8). Peterson (9) reviewed impaired driving cases in Washington State involving gabapentin and concluded that “gabapentin is a commonly encountered drug that is capable of causing driving impairment”.

Pregabalin was developed for its improved pharmacokinetic properties over those of gabapentin. Gabapentin displays saturable absorption kinetics thereby limiting its systemic exposure (10). Pregabalin’s oral bioavailability is approximately...
90% and is independent of dose and frequency of administration (11). Both gabapentin and pregabalin are predominantly excreted unchanged in urine (≥ 98%) (10).

A variety of analytical methods have been developed for the measurement of gabapentin and pregabalin in blood and urine including liquid chromatography–tandem mass spectrometry (LC–MS–MS) (12–14), gas chromatography (GC)–MS (9,15), GC (16), high-performance liquid chromatography (HPLC) (17,18), and capillary electrophoresis (19).

Although gabapentin and pregabalin are widely prescribed by pain management specialists (20), there has been little information published on their detection and measurement in urine of chronic pain patients. This study reports concentration and prevalence data for gabapentin and pregabalin in urine of chronic pain patients.

Experimental

Subjects and specimens

A total of 57,542 urine specimens were collected over the period of November 24, 2009, through May 2010 from 231 pain clinics located in 19 states (AL, FL, GA, IL, KY, LA, MD, MO, MS, NE, NJ, NV, OH, SC, TN, TX, NC, NY, and VA). The specimens were tested by Aegis Sciences (Nashville, TN) for a range of prescribed and illicit drugs. Specimens that confirmed positive for gabapentin and/or pregabalin were assembled into a database containing only test results. No patient information was included. All specimen data were encoded with a study identifier to protect the patient’s confidentiality. No medication history was available for interpretation of results. The protocol for this study was approved by the Essex Institutional Review Board (Lebanon, NJ).

LC–MS–MS analyses

All specimens were analyzed simultaneously for gabapentin and pregabalin directly (without screening) by a validated LC–MS–MS procedure. Gabapentin was purchased from Sigma Aldrich (St. Louis, MO) and pregabalin was provided by Pfizer (Groton, CT). Gabapentin-d₄ (Medical Isotopes, Pelham, NH) was used as the internal standard for both pregabalin and gabapentin. Identification and quantitation of the target analytes was performed with an Applied Biosystems 3200 tandem MS interfaced with a Shimadzu LC-20AD HPLC. The mobile phase was 10 mM ammonium acetate, 0.1% formic acid HPLC water, and 0.1% formic acid acetonitrile. The HPLC column was a Restek Pinnacle DB C₁₈ (3 μm, 100 × 2.1 mm). All analyses were performed with electrospray ionization operating in positive mode. The optimum ionization conditions were as follows: curtain gas (nitrogen), 18 psi; heated nebulizer temperature, 600°C; gas 1 (nitrogen), 70 psi; and gas 2 (nitrogen), 60 psi. In order to establish the appropriate multiple reaction monitoring (MRM) conditions for individual compounds, solutions of standards in methanol/water (50:50, v/v) were infused into the MS, and the declustering potential (DP), collision gas pressure and collision energy (CE) were optimized for the selected transitions. Data acquisition, peak integration, and calculation were performed by a computer workstation running the Analyst 1.4.2 software. Transition ions monitored were as follows (quantitative ions are underlined): gabapentin, 172 → 137 and 172 → 95; gabapentin-d₄, 176 → 158; and pregabalin, 160 → 142 and 160 → 97. The limit of quantitation (LOQ) and upper limit of quantitation (ULOQ) were 2.5 and 1000 µg/mL, respectively, for both analytes. The LOQ was determined by serial dilution of a fortified urine sample. Criteria for setting the LOQ included 1. response for LOQ had to be > 10x signal/noise; 2. response had to meet all qualitative criteria; and 3. quantitation had to be within ±20% of the target concentration. The ULOQ had to meet all qualitative criteria and be within ±20% of the target concentration.

Inter-run imprecision (%CV) and accuracy (% deviation from target concentration) of control samples prepared in urine containing 5 and 100 µg/mL of each analyte were as follows: 2.2%, 1.7% imprecision and −10.0%, −15.2% accuracy for gabapentin (n = 8); and 3.6%, 2.9% imprecision and 10.0%, 2.3% accuracy for pregabalin (n = 8), respectively.

General criteria for the identification and measurement of all analytes were as follows: 1. relative retention time (analyte to internal standard) difference was required to be within ±0.01 compared to the relative retention time of the analyte to internal standard of the calibrator; or the absolute retention time of the analyte in the sample had to be within 3% of the analyte in the calibrator; 2. product ion ratios calculated for the analytes and internal standards had to be within ±20% of those obtained from the corresponding substances in the calibrator; 3. control samples had to measure within ±20% of their in-house determined mean concentration; and 4. drug-free controls could not have analytes above the LOQ. All quantitative data for drugs and metabolites that met identification and quantitation (≥ LOQ) criteria were included in this report.

Table I. Gabapentin and Pregabalin Prevalence, Percent Positivity, and Concentrations Measured in 57,542 Pain Patient Urine Specimens

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Number of Positive Specimens</th>
<th>Percent Positive Specimens</th>
<th>Mean ± SEM (µg/mL)</th>
<th>Median (µg/mL)</th>
<th>Range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>7013</td>
<td>12.2</td>
<td>430.9 ± 8.3</td>
<td>259.8</td>
<td>2.5–35345</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>4799</td>
<td>8.3</td>
<td>183.9 ± 3.6</td>
<td>108.0</td>
<td>2.5–6892</td>
</tr>
</tbody>
</table>

Results and Discussion

Gabapentin was identified in 7013 specimens obtained from 57,542 pain patients (12.2% prevalence) during an approximately 6-month period starting in late November 2009 (Table I). Pregabalin was identified in 4799 patients (8.3% prevalence) over the same period. Interestingly, 249 specimens were identified that con-
tained both drugs. The mean (range) and median concentrations of gabapentin and pregabalin in specimens containing both drugs were 361.0 (2.5–5827) and 188.7 µg/mL and 186.9 (2.8–2267) and 116.0 µg/mL, respectively. Because neuropathic pain treatment guidelines recommend combination therapy using drugs with different mechanisms of action, it seems unlikely that practitioners would routinely prescribe both gabapentin and pregabalin (1–3). The presence of both drugs may instead represent a change in therapy from one agent to the other. The half-lives of gabapentin \( t_{1/2} = 5.9 \) h (21) and pregabalin \( t_{1/2} = 4.6–6.8 \) h (11) are relatively short; however, because abrupt discontinuation may trigger withdrawal symptoms, changing therapy would typically necessitate reducing the dose of initial drug while escalating the dose of the replacement drug over at least one week. In such cases, it seems plausible that patients could test positive for both drugs. Alternatively, presence of both drugs might indicate medication dependence or misuse.

As shown in Table I, urine concentrations of gabapentin and pregabalin varied across a broad concentration range. Both the mean and median concentrations of gabapentin were greater than twofold higher than pregabalin. This is generally consistent with the relative potency of these drugs. The recommended dose for gabapentin is 900–1800 mg/day given in three divided doses, whereas the recommended dose of pregabalin for patients with normal renal function is 150–600 mg/day given in two or three divided doses.

Conclusions

Gabapentin and pregabalin represent a novel class of analgesic drugs that are broadly prescribed for treatment of chronic neuropathic pain. Both drugs are eliminated largely unchanged by renal excretion. This study documented the prevalence and concentration of both drugs in urine specimens of chronic pain patients. Generally, gabapentin concentrations were greater than twofold higher than pregabalin, consistent with their relative potencies. Interestingly, some patients were identified whose specimens were positive for both drugs.

References


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