A non-fatal self-poisoning attempt with sildenafil

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Introduction

Sildenafil
- 1-[(3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-]
d)pyrimidin-5-yl)-4-ethoxyphenyl][sulfonyl]-1-methylpiperazine
- Phosphodiesterase type 5 inhibitor
- Used for treatment of pulmonary hypertension (Revatio®) and erectile dysfunction (Viagra®)
- Not generally known for its use as a self-poisoning drug
- Reports of intoxication cases have been described including some with a lethal outcome

Case report
- 56-year-old man
- Claimed to have undertaken an unsuccessful suicide attempt by ingestion of 65 tablets of 100 mg sildenafil
- Arrived in the emergency room with severe vomiting and symptoms of blurred vision
- Sinus tachycardia of 100 bpm
- No signs of hypotension or priapism
- Supportive care was given

Methods

Development and validation of a high performance liquid chromatography - photodiode array method to quantify the sildenafil level in serum

HPLC system: Agilent 1100/1200 series
HPLC column: Agilent ZORBAX Eclipse Plus C8, 3.0 x 150 mm, 3.5 µm particle size
Column temp.: 40°C
Gradient elution
- Solvent A: 10 mM phosphate buffer, pH 2.3
- Solvent B: 10 mM phosphate buffer pH 2.3: acetonitrile, 2:8
PDA detection at 225 nm

Results

Experimental results
- Limit of detection: 0.008 µg/mL
- Linearity: from 0.025 to 2.5 µg/mL
- 10-fold dilution integrity: 97 ± 10%

<table>
<thead>
<tr>
<th>Target conc. (µg/mL)</th>
<th>Intra-day (n=5)</th>
<th>% error</th>
<th>Inter-day (n=6)</th>
<th>Recovery%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.025</td>
<td>0.029 ± 0.0031</td>
<td>8.3</td>
<td>0.025 ± 0.0031</td>
<td>12.9 ± 1.3</td>
</tr>
<tr>
<td>0.075</td>
<td>0.068 ± 0.0045</td>
<td>7.8</td>
<td>0.071 ± 0.0038</td>
<td>9.2 ± 0.8</td>
</tr>
<tr>
<td>0.250</td>
<td>0.226 ± 0.0015</td>
<td>7.6</td>
<td>0.240 ± 0.0033</td>
<td>7.7 ± 3.9</td>
</tr>
<tr>
<td>2.000</td>
<td>1.831 ± 0.0025</td>
<td>10.2</td>
<td>2.008 ± 0.0047</td>
<td>6.9 ± 0.4</td>
</tr>
</tbody>
</table>

Validation parameters
- % error
- Recovery

Patient results

Multiple serum specimens of the patient collected over 3 days
- Confirmation of the diagnosis of sildenafil intoxication
- Study of sildenafil clearance

- First-order kinetics
- Biological half-life: ~4.2 hours

Discussion

- Full method validation according to European Medicine Agency guidelines
- Highest reported serum conc.: 22.2 µg/mL
  >>> Therapeutic peak conc. after a single oral dose of 100 mg: 0.5 µg/mL
  >>> Conc. fatal case report: 6.3 µg/mL
- Half-life (4.2 h) in accordance with literature data (range: 1.4 – 4.5 h)
- Overdose pharmacokinetics similar to pharmacokinetics after therapeutic doses
- No good correlation between administered dose and clinical outcome
  o Importance of pre-existing risk factors
  o Possible drug interactions

Conclusion

- Highest sildenafil dose ingested, resulting in the highest serum concentration level ever reported
- High tolerance in this patient: few symptoms and only moderate supportive therapy needed for recovery without sequelae
- Unofficial sale of sildenafil and variants, and exponential increase in online pharmacies remain a major concern, especially for patients with pre-existing comorbidities or multiple drug intake

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