NEW DRUG: Tapentadol (Nucynta®)

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In the March 2009 ToxTalk, Waugh and Kraner described tapentadol as a new centrally acting oral analgesic developed by Johnson & Johnson that was approved by the FDA in November 2008 for the treatment of moderate and severe acute pain. In June 2009, the DEA listed tapentadol as a schedule II drug which then became available as Nucynta® for prescription on the US market in immediate-release oral doses of 50, 75, and 100 mg. Reportedly, tapentadol is structurally similar to tramadol and has a potency between that of tramadol/codeine and morphine. The single, parent compound acts as both a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor. Its dual mode of action provides analgesia at similar levels of more potent narcotic analgesics such as hydrocodone and oxycodone with more tolerable side effects. Although Waugh and Kraner suggested tapentadol would have to be detected as a trimethylsilyl derivative, both the Alabama Department of Forensic Sciences and the Los Angeles County Department of Coroner detected tapentadol in their casework utilizing a general basic drug screen with commonly employed instruments such as GC/NPD and GC/MS.

General Information

IUPAC name: 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrochloride
Common name: Tapentadol or Nucynta®
Chemical formula: C_{14}H_{23}NO
Molecular weight: 221.339 g/mol
CAS number: 175591-23-8
Rx dosage: 50, 75, 100 mg tablets
Availability: 1 mg/ml methanol solution purchased from Cerilliant® Corp. (Round Rock, TX), T-058

Toxicology

Extraction: N-butyl chloride L/L basic drug extraction with a 0.1 N HCL acidic back extraction
Detection: GC/NPD and GC/MS
Ions: 58, 107, 221, 133 m/Z
Elution order: Bupropion, Tapentadol, Meperidine, Fluoxetine, Diphenhydramine, Tramadol

Case Studies

Alabama Postmortem Case Study

A 19 year old female decedent (5’10”, 80 kgs), newly married (~3 months), was found unresponsive in the residence by her husband after returning from a day of work. The husband stated that she was taking some unknown
OTC medicine for allergies. Medications bottles belonging to her husband (temazepam, venlafaxine, tapentadol, pregabalin, tizanidine, and baclofen) were found at the scene, but no information as to how full/empty was provided. An autopsy was performed and the pathologist noted no trauma, pulmonary edema, froth in the upper and lower airways and bronchopneumonia. Autopsy specimens were submitted to the laboratory and the following positive toxicology results were obtained:

<table>
<thead>
<tr>
<th>Subclavian Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>0.059 ug/ml</td>
</tr>
<tr>
<td>Carboxy-THC</td>
<td>0.0073 ug/ml</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Not Detected</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>*2.0 ug/ml</td>
</tr>
</tbody>
</table>

*Detected by GC/MS prior to the quantitation performed by NMs Labs, Willowgrove, PA

The cause of death was determined to be multiple drug toxicity; the manner of death was ruled an accident.

**Los Angeles Postmortem Case Study**

A 45 year old male decedent (5’9”, 81 kgs) was found unresponsive in his residence after a night of drinking with friends. He was on several pain medications due to an accident he sustained six months prior to his death. An autopsy was performed and was unremarkable. Autopsy specimens were submitted to the laboratory and the following positive toxicology results were obtained:

<table>
<thead>
<tr>
<th>Heart Blood</th>
<th>Femoral Blood</th>
<th>Vitreous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>0.18 g%</td>
<td>0.19 g%</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>+&lt;0.10 ug/ml</td>
<td>---</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.24 ug/ml</td>
<td>---</td>
</tr>
<tr>
<td>Nordiazepam</td>
<td>0.38 ug/ml</td>
<td>---</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0.20 ug/ml</td>
<td>---</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>0.13 ug/ml</td>
<td>---</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>*~0.44 ug/ml</td>
<td>*~0.27 ug/ml</td>
</tr>
</tbody>
</table>

*GC/NPD methodology not completely validated.

The pathologist determined the cause of death to be multiple drug intoxication and the manner of death to be an accident.

**Discussion**

Tapentadol is a new analgesic used in pain management which has recently been encountered in at least two Toxicology Laboratories. Following oral or IV administration of 60 mg tapentadol, maximum blood concentrations were 0.05 ug/ml (0.027 – 0.073) and 0.30 ug/ml (0.251-0.349), respectively. Efficacy of tapentadol for pain relief was in the range of 0.005-0.30 ug/ml.

The tapentadol quantitation in the Alabama case study was performed by NMS Labs with LC/MS/MS technology and a calibration range of 0.0005-0.25 ug/ml. The tapentadol measured in the subclavian blood (2.0 ug/ml) of the case was more than six times that of the cited clinical therapeutic concentration. This level along with the autopsy findings led the pathologist to declare the case an overdose and the manner an accident.

The Los Angeles case study measured tapentadol at ~0.44 and ~0.27 ug/ml, heart and femoral blood respectively. Although these levels appear to be in the higher edges of a clinical therapeutic range, it may represent what will be determined as a tapentadol postmortem therapeutic concentration with future casework. The concentration differences between the central and peripheral blood may represent some postmortem redistribution, but again, more casework is needed. Overall, the case was determined to be a multiple drug intoxication due to the various respiratory depressants (ethanol, cyclobenzaprine, nordiazepam, oxycodone, and tapentadol) detected and the mode as an accident.

Overall, although tapentadol can be detected with LC/MS/MS technology, it can easily be seen with a basic liquid/liquid drug extraction and detected with commonly employed instruments such as GC/MS and GC/NPD. As there are more cases with tapentadol, the delineation between therapeutic and toxic/lethal will become more apparent and these two case examples may need to be re-evaluated in regards to mode of death.

**References**