Plasma levels and cerebrospinal fluid penetration by duloxetine in a patient with a non-fatal overdose during a suicide attempt

Received 4 June 2009; Reviewed 3 July 2009; Revised 8 July 2009; Accepted 12 July 2009; First published online 6 August 2009

Duloxetine is a potent and selective inhibitor of serotonin and norepinephrine reuptake with weak activity on dopamine reuptake (Wong et al. 1993). Daily doses of 60 mg are effective in the acute treatment of major depression. Duloxetine is extensively metabolized by cytochrome P450 isoenzymes (CYP) 1A2 and to a lesser extent 2D6 (Lobo et al. 2008) to numerous non-active metabolites. Maximum plasma concentration occurs after 6 h, steady-state within 3 d and the mean terminal half-life is 12 h.

Fatal outcomes have been reported for acute overdoses as low as 1000 mg, and symptoms of duloxetine overdose are well described. However, information about plasma levels of duloxetine and corresponding cerebrospinal fluid (CSF) levels providing information about its CSF penetration is lacking. We therefore report the case of a 30-yr-old female patient who intoxicated herself with different psychotropic agents, including duloxetine.

Case study

Mrs L. was a 30-yr-old patient suffering from a major depressive episode (ICD-10: F32.2) as well as an emotionally unstable personality disorder (ICD-10: F60.31). She had also been diagnosed with multiple sclerosis.

During a suicide attempt, she ingested a total amount of 1680 mg duloxetine, 380 mg pipamperone, and 250 mg amitriptyline 6 h before she was admitted to our emergency department. She was found unconscious with foam around the mouth suggesting a seizure. Initially she was found to be somnolent, but responded appropriately when addressed. Within the next few hours she developed a delirious syndrome with agitation and hallucinations. Encephalitis was excluded using MRI and lumbar puncture, the latter showing a slight elevation of the WBC count (10 leukocytes/ml). After the patient admitted intoxication, the plasma levels of the ingested drugs as well as CSF levels were measured about 20 h after ingestion (see Table 1).

Duloxetine plasma levels were >2000 ng/ml, whereas the CSF level was 15 ng/ml. After a 24-h period of monitoring she recovered well and was able to be committed for psychiatric treatment. She was discharged 6 wk later in a stable psychiatric condition.

Discussion

There are very few papers that have reported cases of duloxetine overdose (Menchetti et al. 2008, Raskin et al. 2003), with highest duloxetine plasma levels of 590 ng/ml being recorded.

Our case demonstrates two remarkable findings: first, although the plasma level of duloxetine was extremely high, the side-effects were comparably low. No significant changes in any blood parameters occurred and vital signs were stable over time. A hyperactive delirious syndrome was more likely to be due to the anticholinergic properties of amitriptyline.

Second, duloxetine’s CSF penetration in the presented case seems to be extremely low. Although a PET study clearly shows that duloxetine blocks the serotonin transporter to a large extent (Takano et al. 2006), the ratio between plasma and CSF levels of >130 indicates a very low CSF penetration by duloxetine, possibly due to a not-yet-understood role of active transporter mechanisms keeping it out of CSF.

In conclusion, duloxetine even at high plasma levels is well tolerated and toxicity seems to be comparably low. The demonstrated low CSF penetration requires more understanding of active transporter mechanisms keeping duloxetine out of, or clearing it rapidly from, the CSF.

Acknowledgements

The authors thank A. C. Parker, M.D., Department of Obstetrics & Gynecology, New York Hospital, Cornell Medical Centre, New York, NY (emeritus), for careful reading of this manuscript.
Statement of Interest

Dr Paulzen and Dr Gründer have received grant support from Eli Lilly, Indianapolis, IN, USA. Dr Gründer has served on the speakers’ bureau of Eli Lilly and Boehringer/Ingelheim, Ingelheim, Germany. Dr Hiemke has received research grants from Sanofi Aventis and Pfizer, Karlsruhe, served as a consultant for Servier and received speakers’ fees from Boehringer/Ingelheim, Eli Lilly, Janssen-Cilag, Lundbeck, Pfizer, Sanofi-Aventis, Servier and Wyeth.

References


Table 1. Plasma and CSF levels of different psychotropic drugs after intoxication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Plasma level (ng/ml)</th>
<th>Therapeutic range (ng/ml)</th>
<th>CSF level (ng/ml)</th>
<th>Plasma/CSF ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>143</td>
<td>80–200</td>
<td>&lt;20</td>
<td>&gt;7</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>&gt;2000</td>
<td>20–80</td>
<td>15</td>
<td>&gt;130</td>
</tr>
<tr>
<td>Pipamperone</td>
<td>500–600</td>
<td>–</td>
<td>250</td>
<td>~2</td>
</tr>
</tbody>
</table>

Michael Paulzen1, Christoph Hiemke2, Gerhard Gründer1

1 Department of Psychiatry and Psychotherapy, RWTH, Aachen University, JARA – Translational Brain Medicine, Aachen, Germany

2 Department of Psychiatry and Psychotherapy, University of Mainz, Mainz, Germany