Lesson of the month: Oxycodone-induced leukoencephalopathy: a rare diagnosis

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Oxycodone-induced leukoencephalopathy is a rare diagnosis that should be considered in unconscious patients with appropriate history. We describe a case of a 57-year-old unconscious woman who required intubation and did not respond to naloxone infusion. The unconsciousness was initially thought to be due to hypoxic brain injury. However, a further review of brain imaging showed characteristic features of oxycodone-induced leukoencephalopathy. We describe the pathological and radiological features of this condition, and provide a concise review of the limited literature on this condition. Accurate diagnosis of this condition will be valuable to clinicians and patients in terms of their medium-term and long-term prognosis, and potential for rehabilitation.

KEYWORDS: Oxycodone leukoencephalopathy, cerebral white matter, toxic leukoencephalopathy, heroin, hypoxic brain injury

DOI: 10.7861/clinmed.2020-0650

Case presentation

A 57-year-old woman was found unresponsive at home. She had allegedly taken 14 tablets of 10 mg oxycodone. She had type 2 diabetes mellitus, depression and panic attacks. She was only on mirtazapine. Her Glasgow coma score was 5/15 (E1V1M3) with hypoxia. She had renal and liver dysfunction. Urine toxicology screen was positive for opiates. An initial computed tomography (CT) of the brain was reported as normal. With a diagnosis of oxycodone overdose, she was intubated and given a naloxone infusion over 48 hours. CT of the brain 2 days later raised the possibility of global hypoxic brain injury. Over the next 10 days, she did not need sedation while intubated and ventilated, and had no gag reflex. In view of possible global hypoxic brain injury, organ donation was considered and spiritual care offered with the assumption that she was dying. Tracheostomy was performed 13 days later and she was stepped down to the stroke unit. Images reviewed by a neuroradiologist confirmed that findings were in keeping with oxycodone overdose. The initial CT showed low attenuation in both cerebellar white matter (WM) and globus pallidi (GPa). Subsequent imaging (Fig 1) showed progression of this low attenuation with pathologic mass effect resulting in tonsillar herniation and mechanical obstruction to cerebrospinal fluid outflow. An interval magnetic resonance imaging (MRI) of the brain showed appropriate evolution of the GPa and bi-cerebellar injury (Fig 2). The combination of cerebellar and GPa injury was suggestive of an acute oxycodone leukoencephalopathy rather than an inflammatory, metabolic or ischaemic insult. Electroencephalography was atypical for hypoxic ischaemic encephalopathy. She had a successful tracheostomy decannulation and percutaneous endoscopic gastrostomy insertion to maintain nutrition. Over the next 2 months she became more alert with significant neurological deficits and continues neurorehabilitation.

Cerebral white matter

The cerebral white matter (WM), with its myelinated axons arranged in tracts or fasciculi, occupies about half of an adult human brain volume with an estimated 100 billion neurones and 135,000 kilometres of axons, equivalent to running about thrice around the globe. It has also been recognised that WM is found within the GM of the cortical mantle and subcortical nuclei (thalamus and basal ganglia).

Toxic leukoencephalopathy

Toxins that disrupt myelin sheath and/or axons include drugs of abuse (heroin and opioids); environmental factors (carbon monoxide), occupational factors (paint) or therapeutics (anti-neoplastic, antimicrobial and immunosuppressives). Interhemispheric and intrahemispheric pathways that serve cognition and emotion (neurobehaviour) are predominantly involved. Hence the most important clinical feature includes a change in mental status. The spectrum of neurobehavioural symptoms and corresponding pathology include mild (confusion or inattention; patchy intramyelinic oedema with preservation of myelin), moderate...
Oxycodone induced leukoencephalopathy

Opioids are lipophilic and accumulate in the lipid-rich myelin sheath when taken in large doses. Oxycodone, a semi-synthetic strong prescription opioid, has an oral bioavailability of 87% (vs morphine at 30%) and attains a maximum plasma concentration under 1 hour with a plasma half-life of 3–4 hours.

The first case series (47 patients) of inhaled heroin pyrolysate-induced WM damage was described in 1982. These patients presented with cerebellar syndrome and CT revealed hypoattenuation in cerebral and cerebellar WM. There are further reports of, predominantly, children presenting unconscious or unresponsive with WM changes in the cerebrum or cerebellum after inadvertent exposure to heroin, morphine or methadone.

One Belgian case report was on a 65-year-old woman who had extensive, symmetrical cerebral WM changes after inadvertently ingesting a high dose of methadone. Oxycodone-associated neurotoxicity was first published in 2010. To the authors’ knowledge, there are nine such cases reported in the literature (summarised in Table 1).

The hallmark of heroin-induced encephalopathy (along with morphine and methadone) is cerebellar involvement due to the affinity of heroin to ‘μ’ receptors that are heavily distributed in the cerebellum. Oxycodone, however, has a high affinity for ‘κ’ receptors that are heavily distributed in the basal ganglia and cerebellum.

Magnetic resonance imaging

The WM involvement tends to be diffuse and symmetrical with characteristic vacuolisation and spongiform changes. Tormoehlen describes the classic MRI findings as symmetrical distribution in the cerebellar and posterior cerebral hemispheres, including the posterior limbs of the internal capsule. Cerbellar dentate nuclei, subcortical ‘U’ fibres in the posterior cerebrum and anterior limbs of the internal capsule are relatively spared.

The feature that is common to oxycodone neurotoxicity is GPa injury (Table 1). The involvement of basal ganglia has also been noticed in other case reports with methadone use. The bilateral symmetry and involvement of two regions (cerebellum and GPa) are strongly suggestive of toxic damage. One has to be aware that GPa injury can also be seen in carbon monoxide poisoning and intravenous heroin abuse.

A further analysis of MRI by Shrot and colleagues in three opioid-related acute brain injury cases showed bilateral symmetrical cerebral WM and cerebellar lesions with involvement of putamen in two of these cases.

Conclusion

Acute neurological presentation in patients ‘being down’ after drug overdose can be incorrectly attributed to hypoxic brain injury. Toxic leukoencephalopathy should be considered in the differential diagnosis. Diagnosis is often achieved with careful consideration of the history, clinical features and imaging findings. There is paucity of case reports on oxycodone leukoencephalopathy, hence the authors felt the need for reporting this case.
### Table 1. Case reports on oxycodone-induced leukoencephalopathy

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Drug causing encephalopathy</th>
<th>Age and sex</th>
<th>Presenting clinical feature</th>
<th>Brain structure(s) involved</th>
<th>Outcome at time of reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales Odia Y (2010)^6</td>
<td>Oxycodone 350 mg and oxycetin 400 mg</td>
<td>46 years M</td>
<td>Respiratory depression and acute hydrocephalus</td>
<td>Cerebellum and GPa</td>
<td>Survived with residual disability</td>
</tr>
<tr>
<td>Beatty CW (2014)^7</td>
<td>Oxycodone 75 mg</td>
<td>14 years F</td>
<td>Altered mental status and decreased respiration</td>
<td>GPa</td>
<td>Survived but with mild disability</td>
</tr>
<tr>
<td>Holyoak AL (2014)^8</td>
<td>Oxycodone and clonazepam</td>
<td>26 years M</td>
<td>Unresponsiveness</td>
<td>GPa and periventricular WM</td>
<td>Tracheostomy; died of another cause soon after</td>
</tr>
<tr>
<td>Ramirez-Zamora A (2015)^9</td>
<td>Oxycodone</td>
<td>Adult</td>
<td>Reduced sensorium</td>
<td>GPa and hippocampus</td>
<td>Persistent neurobehavioral symptoms</td>
</tr>
<tr>
<td>Middlebrooks EH (2017)^10</td>
<td>Oxycodone (nasal)</td>
<td>29 years F</td>
<td>Acute confusion, bradykinesia and early hydrocephalus</td>
<td>Caudate, putamen, GPa, and internal and external capsule</td>
<td>Residual parkinsonism at discharge</td>
</tr>
<tr>
<td>Duran D (2017)^11</td>
<td>Oxycodone</td>
<td>38 years M</td>
<td>Unresponsiveness</td>
<td>WM of supratentorial brain and right cerebellum</td>
<td>Died</td>
</tr>
<tr>
<td>Wheaton T (2019)^2</td>
<td>Oxycodone</td>
<td>10 month F</td>
<td>Unresponsiveness</td>
<td>Cerebellum and caudate nucleus</td>
<td>At 33 months had some neurological signs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 years M</td>
<td>Unresponsiveness</td>
<td>Cerebellar and cerebral WM lesions</td>
<td>Survived with residual disability</td>
</tr>
</tbody>
</table>

AKI = acute kidney injury; BG = basal ganglia; F = female; GPa = globus pallidi; M = male; WM = white matter.

### Conflicts of interest

Dr Mehol Patel is on the editorial board of Clinical Medicine.

### References


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