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Active chlordiazepoxide metabolites in a patient needing life support after treatment of alcohol abstinence

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Introduction

It is important to treat alcohol withdrawal syndrome to ease symptoms and avoid severe complications including seizures and delirium tremens. Benzodiazepines with a long half-life are often the preferred treatment. In a meta-analysis from 2011,[1] chlordiazepoxide tended to perform better than other benzodiazepines and is accordingly often used. Chlordiazepoxide has several pharmacologically active metabolites.[2] The first is desmethylichlordiazepoxide, which is further metabolized to demoxepam, nordazepam (synonymous with desmethyldiazepam), and oxazepam.[3] In healthy volunteers, steady-state concentrations of chlordiazepoxide are reached after 1-2 days, whereas demoxepam and nordazepam reach steady-state concentrations after 3-5 days following repeated doses of 30 mg daily.[3] The elimination half-life of nordazepam may be as long as 4-6 days. In patients with liver cirrhosis, clearance of chlordiazepoxide is 3-fold lower than in healthy subjects, and desmethylichlordiazepoxide is formed and eliminated significantly slower after a single dose of 50 mg chlordiazepoxide.[4] Thus, formation and elimination of demoxepam, nordazepam and oxazepam may also be delayed in hepatic cirrhosis and give rise to accumulation and risk of toxicity when the drug is given in repeated doses, which is often the case in patients with alcohol withdrawal syndrome.

Although the decreased clearance of chlordiazepoxide in liver cirrhosis was shown in the 1970s,[5] only two previous case reports have described long-term sedation lasting up to 28 days after treatment of alcohol withdrawal with chlordiazepoxide in therapeutic doses.[5, 6] Both cases concerned chronic alcoholics with liver cirrhosis. In one of them, toxic concentrations of chlordiazepoxide was measured two to seven days after cessation of chlordiazepoxide treatment.[5] However, no metabolites were measured.[5] To our knowledge, no chlordiazepoxide metabolites have been measured, thus far, in cases of prolonged sedation caused by therapeutic doses of chlordiazepoxide used for alcohol abstinence. Here, we present a case of long-term sedation requiring mechanical ventilation, in which we found nordazepam in therapeutic levels three weeks after ceasing chlordiazepoxide treatment.

Case description

This case report concerns a 54-year-old woman with a diagnosis of alcohol abuse, depression, anxiety, hepatitis C, and changes on computed tomography (CT)-scan compatible with liver cirrhosis. The patient was initially admitted for alcohol detoxification at the psychiatric hospital in 2019, where she was given 250 mg chlordiazepoxide and was discharged the next day. One week later (Day 1, Table 1), she was readmitted to the psychiatric hospital for treatment of alcohol abuse and depression. The patient became increasingly confused and anxious and on day four, treatment with chlordiazepoxide was initiated due to abstinence symptoms. On day four to seven, a cumulative dose of 950 mg chlordiazepoxide was given and phenobarbital was added on day seven because of upper extremity tremor, which was interpreted as withdrawal symptoms. On day 8, the
The patient was transferred to the department of neurological diseases because of deteriorating consciousness level. Ischaemic stroke and infection in the central nervous system were suspected but excluded by cerebral CT scan and lumbar puncture. A cerebral magnetic resonance scan was compatible with Wernicke's encephalopathy, and serum-ammonia was 117 µmol/l (upper physiological limit 50 µmol/l). Thiamine treatment was initiated, and due to continued restlessness, a total dose of 300 mg chlordiazepoxide was administered again on day 11-12 yielding a total dose of 1250 mg given over eight days. Phenobarbital was continued until day 13 with a cumulated dose of 1600 mg. On day 16, the patient was admitted to the intensive care unit due to reduced consciousness and tachypnoea. Glasgow coma score (GCS) was three. She was intubated, and treatment of liver coma and aspiration pneumonia was started. The results of biochemical liver parameters were INR 1.3, bilirubin 9 µmol/l, ALAT 19 U/l, and gamma-glutamyltransferase 202 U/l at this time. Serum-phenobarbital was 11.8 mg/l (therapeutic range 10-40 mg/l) [7]. Despite using only small doses of propofol and remifentanil, the patient was difficult to wake up. On day 20, serum-ammonia had decreased to 49 µmol/l. On day 22, benzodiazepine overdose was suspected as the cause of the prolonged sedation, because urine drug screens had been positive for benzodiazepines on several occasions during the admission. Small refract doses of flumazenil were given and improved the patient’s level of consciousness. It was chosen not to use continuous flumazenil infusion, and the patient was mechanically ventilated until day 34. During the course, she was suffering from restlessness, especially nocturnal, which was treated with propofol and quetiapine. The highest measured values of INR, ALAT and gamma-glutamyltransferase during the stay in the intensive care unit were 1.4 U/l, 51 U/l, and 449 U/l, respectively. The patient was discharged from the intensive care unit on day 42 in her usual condition.

When mechanical ventilation was stopped on day 34, whole blood samples were sent to the Department of Forensic Medicine, Aarhus University, where a toxicological analysis, which is routinely used to detect drugs in forensic cases, was performed. The blood sample was screened for toxic compounds, illegal and legal drugs and some of their metabolites using protein precipitation followed by ultra-performance liquid chromatography with high-resolution time-of-flight mass spectrometry (UPLC-HRTOF-MS). The method can detect approximately 700 substances of which the 225 most toxicologically relevant drugs and metabolites have been validated [8]. Detected drugs including demoxepam, nordazepam and oxazepam were quantified by ultra-performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS) using validated methods. Chlordiazepoxide was no longer present in the patient on day 34, but the metabolites demoxepam, nordazepam and oxazepam were detected at concentrations of 0.26 mg/kg, 0.15 mg/kg, and 0.0077 mg/kg, respectively. The concentration of nordazepam was thus within the therapeutic range based on a blood/plasma ratio of 0.6, and reference values from 0.2-0.8 mg/l in plasma, [7] whereas the concentrations of demoxepam and oxazepam were below therapeutic level (therapeutic range 0.5-0.74 mg/l [7], and 0.2-1.5 mg/l, respectively). Furthermore, subtherapeutic concentrations of phenobarbital (1.5 mg/kg), propofol (1.1 mg/kg) and metoprolol (0.015
mg/kg) were detected. The therapeutic ranges of propofol and metoprolol are between 2-8 mg/l, and 0.035-0.5 mg/l, respectively.[7]

Written informed consent to publish the case description was obtained from the patient.

Discussion

We present a case report of a 54-year-old woman with alcohol withdrawal syndrome and hepatic impairment, treated with repeated cumulative doses of chlordiazepoxide and phenobarbital that expressed symptoms compatible with chlordiazepoxide intoxication. The main finding is that the pharmacologically active metabolites of chlordiazepoxide that may contribute to sedation were detected in absence of the parent drug more than two weeks after the last administration. In the case report by Maxa et al.,[5] a patient required flumazenil infusion for 9 days after receiving a total therapeutic dose of 650 mg chlordiazepoxide, and the authors measured toxic concentrations of chlordiazepoxide four to six days after initiation of treatment. They reckoned that the prolonged course was due to active metabolites, although they could not measure them. Our finding supports that hypothesis.

In the present case, the need for mechanical ventilation and acute tracheal intubation of the patient arose four days following chlordiazepoxide discontinuation. Interestingly, this lag time corresponds well to observations in the paper by Maxa et al.[5] and in a previous case report of a younger patient receiving a chlordiazepoxide overdose (5.2 g) over four days.[2] This latter patient[2] had to be intubated for four days starting 4.5 days after the last dose of chlordiazepoxide. At the point of intubation, the author measured chlordiazepoxide and metabolites, and found only demoxepam in toxic concentrations decreasing to non-toxic levels after seven days. Nordazepam was in therapeutic levels at both measurements, and the chlordiazepoxide concentration was subtherapeutic. The authors concluded that toxicity was mainly due to demoxepam. In our case, demoxepam had returned to subtherapeutic levels at the time that sedation subsided, while nordazepam was still at therapeutic levels. Thus, our finding also agrees with the hypothesis of demoxepam as a major contributor to toxicity of chlordiazepoxide, while nordazepam may be present in a steadier concentration due to its longer half-life.

It is a limitation of our case-report that we only had a single measurement of chlordiazepoxide and its metabolites. Furthermore, our screening did not encompass desmethyclordiazepoxide. Factors including hepatic encephalopathy, aspiration pneumonia and concomitant treatment with phenobarbital may have contributed to the decreased consciousness level of the patient in our case report. A post-hoc analysis of cirrhotic patients has indicated that 2-10 days’ use of benzodiazepines is associated with a markedly increased risk of developing hepatic encephalopathy.[9] Thus, benzodiazepine toxicity could have elicited a vicious circle with hepatic encephalopathy leading to more severe sedation, aspiration pneumonia, aggravation of liver function and decreased elimination of chlordiazepoxide metabolites. However, the normal serum ammonia,
normalization of the patient’s cerebral condition after the course, and the observed effect of flumazenil several days prior to the resolution of unconsciousness speaks in favour of benzodiazepines as a main cause of prolonged sedation in our patient. The combination of phenobarbital and chlordiazepoxide may have worsened the symptoms of the patient as previous reports have shown that severe toxicity of chlordiazepoxide overdose is infrequent, but more common when combined with phenobarbital.[10] The effect is mediated through additive adverse effects such as sedation that potentially occurs when chlordiazepoxide and phenobarbital is used concomitantly. However, phenobarbital was in the lower range of therapeutic levels at the beginning of the ICU stay and decreased to negligible concentrations on day 34. Therefore, although we can only assume that phenobarbital is a minor contributor, we cannot rule out a potential pharmacodynamic interaction between the metabolites of chlordiazepoxide and phenobarbital as a contributor to the overall clinical perspectives (i.e. sedation and loss of consciousness) reported in this patient. Finally, we did not test for genetic polymorphisms of CYP enzymes responsible for the metabolism of chlordiazepoxide. However, we could not find any literature supporting that genetic polymorphisms of CYP enzymes play a role in patients with liver cirrhosis, and therefore we do not expect that this is of any clinical relevance in the present case history.

We do not know how commonly prolonged sedation due to chlordiazepoxide administration occurs. This drug is the oldest benzodiazepine on the market, and the use for treatment in alcohol abstinence is widespread, often occurring in chronic alcoholics who are at risk of undiagnosed hepatic malfunction. As we were only able to find two other reported cases with prolonged sedation suspected as a side effect to abstinence treatment, we may suspect that the role of chlordiazepoxide in chronic alcoholics progressing to coma may be underdiagnosed and attributed to other factors. Clinical studies with continuous measurements of chlordiazepoxide and active metabolites would be interesting to clarify the impact of chlordiazepoxide toxicity in these patients.

Conclusion

The present case report underlines the need for careful administration of therapeutic doses of chlordiazepoxide in patients with impaired hepatic metabolism. Symptoms that are potentially life-threatening, and need acute supportive life-saving treatment, may peak several days after ceasing administration and measurement of chlordiazepoxide metabolites are pivotal in order to establish the diagnosis.

Conflicts of interest

The authors have no conflicts of interest to declare.
References

Table 1. Sequence of events during the admission. Cpx: Chlordiazepoxide.

<table>
<thead>
<tr>
<th>Day</th>
<th>Cpx dose</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Admission to psychiatric hospital</td>
</tr>
<tr>
<td>4-5</td>
<td>550 mg</td>
<td>Abstinence score 5</td>
</tr>
<tr>
<td>6</td>
<td>250 mg</td>
<td>Phenobarbital added</td>
</tr>
<tr>
<td>7</td>
<td>150 mg</td>
<td>Phenobarbital continued</td>
</tr>
<tr>
<td>8-9</td>
<td>300 mg</td>
<td>Transfer to Department of Neurology. Serum-ammonia 117 µmol/l</td>
</tr>
<tr>
<td>11-12</td>
<td>300 mg</td>
<td>Phenobarbital stopped. Accumulated dose 1600 mg</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>Mechanical ventilation. Phenobarbital 11.8 mg/L (within therapeutic range)</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>Treatment of liver coma initiated</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>Ammonia 49 µmol/l (within normal range).</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>Shortly awakened by flumazenil bolus</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>Unsuccessful trial of extubation → re-intubation. -&gt;</td>
</tr>
<tr>
<td>34</td>
<td></td>
<td>Extubation. Toxicological analysis</td>
</tr>
<tr>
<td>42</td>
<td></td>
<td>Discharge from the intensive care unit</td>
</tr>
</tbody>
</table>