CASE REPORT

N-Acetylcysteine for the Treatment of Clove Oil-Induced Fulminant Hepatic Failure

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ABSTRACT

We present a 3-month-old female who developed fulminant hepatic failure after ingesting less than 8 mL of clove oil. Initial treatment involved gastrointestinal decontamination, supportive measures, and admission to hospital. She subsequently developed fulminant hepatic failure and was treated with intravenous N-acetylcysteine (N-AC) according to a protocol used for acetaminophen poisoning. Over the next 72h her liver synthetic function and clinical status improved, and she made a complete recovery. Previous reported cases of clove oil toxicity and the potential role of N-AC therapy are reviewed.

Key Words: Eugenol; Acetylcysteine; Poisoning; Liver failure.

INTRODUCTION

Clove oil is one of many essential oils known to be potentially toxic to humans. It is ubiquitous in foods and pharmaceutical products, and its active component eugenol is frequently used in dental procedures as an antiseptic and analgesic. Concentrated clove oil is widely available without a prescription in pharmacies.
and grocery stores, as well as health food and pet stores. Its marketed uses include use as a topical dental analgesic, an aromatherapy agent, food flavoring agent, and for the home anesthesia of tropical fish. It is typically found in bottles of 8 mL but can be obtained in much larger quantities (30–60 mL). Toxicity in children has been reported with doses of less than 5 mL. We report a case of clove oil ingestion by an infant resulting in fulminant hepatic failure that was treated with N-acetylcysteine.

**CASE REPORT**

A 3-month-old, 6 kg female was given no more than 8 mL of clove oil (volume of container was 8 mL; some had spilled on her clothing) to drink by her 26-month-old brother at approximately 2000 hours the day of admission. She was transported by ambulance to the local Emergency Department (ED) and became progressively less responsive en route. She arrived in the ED within 60 mins of ingestion, where she was found to be obtunded with grunting respirations. She was endotracheally intubated, and 1 gm/kg of activated charcoal was administered by nasogastric tube. Laboratory tests including CBC, electrolytes, urea, and creatinine were initially normal. Hepatic transaminase levels and coagulation tests were not performed at the initial center. An acetaminophen level was checked, however, and was below the detection threshold (reported as <66 μM). She was transferred to a pediatric quaternary care centre and admitted to the Intensive Care Unit within 4h of ingestion.

Her initial course in ICU was uneventful, and she was extubated at 16h postingestion. At this point her serum transaminase levels were normal, but she exhibited evidence of coagulopathy (see Fig. 1 and Table 1). She was transferred to a pediatrics ward, but approximately 26h postingestion she was noted to be unresponsive and was found to be hypoglycemic (glucose <1.1 mmol/L). Bloodwork drawn at that time showed acute hepatic injury and an evolving coagulopathy. She was transferred back to the ICU and given 60 mL of fresh frozen plasma, 1 unit of cryoprecipitate, and 2 mg of vitamin K intravenously.

The ICU physicians consulted the Regional Poison Information Centre and were advised to continue supportive care and to give the patient an infusion of intravenous N-AC according to the standard 20h protocol used for acetaminophen poisoning (1). This therapy was begun 32.5h postingestion, and the third stage of the infusion (6.25 mg/kg/h) was continued until her INR had fallen below 2.0, for a total of 52h of N-AC therapy. She did not require reintubation but did receive a transfusion of packed red blood cells because her hemoglobin fell to 63 g/L (from initial value of 115 g/L). The patient had several black stools, at least one of which tested positive for hemoglobin, and so she was treated with ranitidine in addition to the other measures. At 67h postingestion she was discharged from the ICU to the Gastroenterology service and recovered steadily thereafter. She was discharged home five days postingestion. The most recent follow-up contact revealed that on her first birthday the patient had recovered completely and showed no ill effects of her clove oil exposure.

**Table 1.** Selected laboratory values for the present case as a function of time.

<table>
<thead>
<tr>
<th>Time postingestion (h)</th>
<th>ALT(U/L)</th>
<th>AST(U/L)</th>
<th>INR</th>
<th>Fibrinogen (gm/L)</th>
<th>pH</th>
<th>HCO ₃ (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>7.36</td>
<td>20</td>
<td>1.13</td>
<td>1.89</td>
<td>7.36</td>
<td>20</td>
</tr>
<tr>
<td>5.5</td>
<td>60</td>
<td>63</td>
<td>1.48</td>
<td>1.89</td>
<td>7.25</td>
<td>24</td>
</tr>
<tr>
<td>16</td>
<td>197</td>
<td>216</td>
<td>1.48</td>
<td>1.89</td>
<td>7.42</td>
<td>18</td>
</tr>
<tr>
<td>26</td>
<td>4683</td>
<td>4990</td>
<td>2.06</td>
<td>1.20</td>
<td>7.39</td>
<td>19</td>
</tr>
<tr>
<td>35</td>
<td>8290</td>
<td>&gt;10000</td>
<td>3.06</td>
<td>1.20</td>
<td>7.42</td>
<td>19</td>
</tr>
<tr>
<td>38</td>
<td>8761</td>
<td>8277</td>
<td>3.86</td>
<td>0.86</td>
<td>7.45</td>
<td>20</td>
</tr>
<tr>
<td>48</td>
<td>6513</td>
<td>4563</td>
<td>3.69</td>
<td>0.76</td>
<td>7.46</td>
<td>23</td>
</tr>
<tr>
<td>62</td>
<td>4747</td>
<td>1732</td>
<td>2.60</td>
<td>0.72</td>
<td>7.47</td>
<td>27</td>
</tr>
<tr>
<td>70</td>
<td></td>
<td></td>
<td>1.69</td>
<td>0.78</td>
<td>7.40</td>
<td>28</td>
</tr>
<tr>
<td>84</td>
<td>4417</td>
<td>633</td>
<td>1.04</td>
<td></td>
<td>7.40</td>
<td>24</td>
</tr>
<tr>
<td>92.5</td>
<td>3245</td>
<td>194</td>
<td></td>
<td></td>
<td>7.40</td>
<td>24</td>
</tr>
<tr>
<td>108</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.40</td>
<td>24</td>
</tr>
</tbody>
</table>

Note: N-AC infusion ran from 32.5 to 84.5h postingestion. ALT, alanine aminotransferase (normal <110); AST, aspartate aminotransferase (<60); INR, international normalized ratio (0.9–1.10); HCO ₃, bicarbonate (17-29); U/L, units per litre. Normal values for fibrinogen 1.6–4.0; pH 7.35–7.50.
The patient’s medical history prior to this incident had been entirely unremarkable. Her antenatal course was normal, and she was born at 39 weeks gestation by elective Caesarean section and had an uneventful postnatal period. The clove oil in question had been purchased by her mother at a local pharmacy for the mother’s personal use. The bottle, which does not have a childproof cap, was stored in the household medicine cabinet from which it was obtained by the patient’s brother.

**DISCUSSION**

There are several reports of local (2–5) and systemic allergic (6,7) reactions to eugenol following dental procedures and topical use. However, there are only three reported human cases of severe toxicity from clove oil: two following ingestion of clove oil by young children (8–10) and one following intravenous administration of clove oil (11). The range of toxic effects seen with clove oil poisoning is demonstrated by these cases (Table 2). Of note, only one of the patients experienced liver damage, and in that case the authors mentioned the potential benefit of N-AC therapy in their discussion but did not report using it in their patient (8).

The mechanism of toxicity of clove oil in humans is incompletely understood but resembles the hepatotoxicity induced by acetaminophen. Animal data suggest that eugenol is metabolized by hepatic cytochrome P-450 enzymes to a quinone intermediate that causes hepatotoxicity (12,13). In vivo studies of the effect of eugenol in rat hepatocytes document depletion of hepatic glutathione (14) and conjugation of eugenol with glutathione (12,15), sulphate (15), and glucuronic acid (15). In a murine model, depletion of hepatic glutathione prior to eugenol administration greatly enhanced the toxicity of eugenol administration (13). Finally, two animal studies demonstrated that the hepatotoxicity of eugenol could be completely prevented by the administration of glutathione (14) or N-AC (15).

While the use of N-AC for the treatment of eugenol-induced hepatocellular necrosis has a strong theoretical basis, we could find no published reports of the use of N-AC for this indication in humans. N-AC is considered standard therapy to prevent and treat hepatotoxicity induced by acetaminophen poisoning and has been used to treat fulminant liver failure secondary to acetaminophen (16) as well as other etiologies (17).

While our patient’s dramatic improvement cannot be ascribed with certainty to the use of N-AC, the

**Table 2.** Reported cases of clove oil toxicity in humans.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient age</th>
<th>Amount and route of clove oil</th>
<th>Toxicity reported</th>
<th>Treatment and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirsch et al. (1990) (10)</td>
<td>32 yrs</td>
<td>unknown amount intravenous</td>
<td>ARDS</td>
<td>supportive care → recovery</td>
</tr>
<tr>
<td>Lane et al. (1991) (9)</td>
<td>7 mos</td>
<td>5 mL oral</td>
<td>CNS depression, amion gap acidosis</td>
<td>late gastric lavage+ETI+ supportive care → recovery</td>
</tr>
<tr>
<td>Hartnoll et al. (1993) (7) and Brown et al. (1992) (8)</td>
<td>2 yrs</td>
<td>5–10 mL oral</td>
<td>CNS depression, amion gap acidosis, fulminant hepatic failure, ? DIC</td>
<td>ETI+supportive care+ coagulation factors → recovery</td>
</tr>
<tr>
<td>Present case</td>
<td>3 mos</td>
<td>&lt;8 mL oral</td>
<td>CNS depression, fulminant hepatic failure, DIC</td>
<td>ETI+supportive care+ N-AC → recovery</td>
</tr>
</tbody>
</table>

ARDS, acute respiratory distress syndrome; CNS, central nervous system; ETI, endotracheal intubation and mechanical ventilation; DIC, disseminated intravascular coagulation; N-AC, N-acetylcysteine.
temporal relationship and biologic plausibility suggested by previous work support a potential role for the use of N-AC in patients with eugenol-induced hepatic injury. Given the similarities between clove oil and acetaminophen-induced liver damage, including the delayed onset of hepatotoxicity, N-AC may have beneficial effects in cases of acute clove oil poisoning. Because N-AC is generally safe and because no other specific therapies are available to treat life-threatening clove oil toxicity, clinicians may wish to consider the use of N-AC in patients with confirmed or suspected clove oil ingestions.

REFERENCES


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