Clinical Relevance and Cost-Savings of Levocarnitine Versus Ammonul in the Management Of Hyperammonemia in a Cancer Patient
The Impact of a Clinical Pharmacist
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ABSTRACT

Background: Hyperammonemia, a relatively uncommon condition characterized by elevated ammonia levels in the blood, presents with varied physiological etiologies that may send patients to the intensive care unit (ICU) with encephalopathy. An immediate decrease in ammonia levels is necessary to avert neurological damage. However, due to the multifaceted nature of hyperammonemia, a definite determination of etiology is not always possible.

Objective: This case report examines the clinical and economic impact of a pharmacist in managing acute hyperammonemia of unknown etiology in a 62-year-old Hispanic man who had recently been diagnosed with metastatic medullary thyroid cancer and associated hypercalcemia. The patient was treated with levocarnitine after the failure of several other treatments.

Results: Levocarnitine therapy controlled the patient’s ammonia levels, which had progressively reached extremely high levels. His mental status, which had deteriorated severely, returned to baseline.

Conclusion: This case illustrates the importance of having a clinical pharmacist in the ICU. The pharmacist’s expertise and knowledge helped avert adverse clinical consequences and promoted considerable cost-savings. This case also shows that levocarnitine may be an effective treatment for certain cases of hyperammonemia-induced encephalopathy with unknown etiology.

Keywords: hyperammonemia, encephalopathy, levocarnitine, clinical pharmacist, case report

INTRODUCTION

Hyperammonemia, a relatively uncommon condition characterized by elevated ammonia levels in the blood, presents with varied physiological etiologies that may require patients’ admission to the intensive care unit (ICU) with encephalopathy. In elevated cases of hyperammonemia, an immediate decrease in ammonia levels is necessary to avert neurological damage. Carnitine is a natural metabolic compound that acts as a carrier molecule for long-chain fatty acids’ transfer from the cytoplasm to the mitochondria, thereby facilitating mitochondrial energy production. A deficiency in carnitine is associated with accumulation of excess acyl-CoA esters, which disrupts intermediary metabolism. Reports have indicated the importance of carefully evaluating anorexic patients with hyperammonemia for carnitine deficiency.

Acute hyperammonemia can lead to significant morbidity and mortality. Hyperammonemia is most often a result of acute liver failure or chronic liver disease but can occur with no hepatic injury. Patients experiencing acute hyperammonemia may present with encephalopathy that ranges from mild mental status deterioration to coma, cerebral edema, brain stem herniation, and even death. When acute hyperammonemia is not associated with acute liver failure, other causes of hyperammonemia should be evaluated, including adverse drug effects, infections, and other unexplainable metabolic disorders. Studies on occurrence and possible causes of nonhepatic hyperammonemia are scanty. The objective of this report is to present the impact of a clinical pharmacist in managing a case of acute hyperammonemia that was treated with levocarnitine after the failure of several other treatments.

CASE REPORT

This case involved a 62-year-old Hispanic man with a past medical history of hypertension and diabetes mellitus, a recent diagnosis of metastatic medullary thyroid cancer (bones and lungs), and hypercalcemia associated with malignancy. Medical records showed control of both hypertension and diabetes. The patient had previously been admitted for worsening rib and back pain, shortness of breath (particularly upon exertion), and a 40-pound weight loss over the past several months; he was ultimately diagnosed with metastatic medullary thyroid carcinoma via bone biopsy and thyroid fine-needle aspiration. However, a computed tomography (CT) scan of the chest, abdomen, and pelvis at that time showed diffuse osteolytic lesions and multiple pulmonary nodules. A magnetic resonance image of the brain was negative for metastatic disease. The patient was to follow up with the oncology service three weeks

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after discharge to initiate therapy with vandetanib (Caprelsa, Genzyme) 300 mg orally daily for treatment of his metastatic medullary thyroid carcinoma.

The patient was readmitted before his appointment with oncology and was prescribed 15-mg extended-release morphine tablets every 12 hours for pain control. He experienced intermittent hypoxia, perhaps from the significant tumor burden in the lungs. He was discharged home with 2 L oxygen for hypoxia. A CT scan for pulmonary embolism was negative, and acid-fast bacillus testing was negative for three samples. Assays for fungal disease were also all negative (including histoplasma, coccidioides, cryptococcus, and blastomyces), and pulmonary function tests were relatively normal despite the patient’s symptoms.

The patient was brought to the emergency department five days after discharge with acute-onset altered mental status, anorexia, continued shortness of breath, and chest pain. The patient’s caregiver said he had been stable post-discharge, but the night prior to this admission, he had been confused and disoriented while making many incoherent statements. The patient complained of nausea and had a reduced oral intake, but he denied any vomiting, change in bowel habit, or change in his baseline rib and back pain. A dietary assessment was done and was consistent with the patient’s condition.

Upon clinical evaluation, the patient weighed 70.8 kg and exhibited appetite change, fatigue, shortness of breath, myalgia, back pain, confusion, tachycardia (117 beats per minute), and rhonchi; he answered questions in a slow and subdued manner. Pertinent lab values are listed in Table 1. He was started on intravenous (IV) 500 mL normal saline bolus for rehydration, lisinopril 10 mg for blood pressure, morphine 2 mg for pain, 4 L oxygen (via nasal cannula), and megesterol acetate 400 mg tablets every 12 hours for pain control. He experienced intermittent hypoxia, perhaps from the significant tumor burden in the lungs. He was discharged home with 2 L oxygen for hypoxia. A CT scan for pulmonary embolism was negative, and acid-fast bacillus testing was negative for three samples. Assays for fungal disease were also all negative (including histoplasma, coccidioides, cryptococcus, and blastomyces), and pulmonary function tests were relatively normal despite the patient’s symptoms.

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**Observation**

On day 3 of admission, an elevated serum ammonia level (160 mcmol/L) was noted from the lab test. Liver function tests did not indicate any liver damage. However, the patient’s mental status increasingly showed a decline, with signs of waxing and waning. Lactulose 20 g two times daily was started for his elevated serum ammonia concentration. Four days later, the patient’s average ammonia level was 159 mcmol/L; morphine was withheld to check for opiate delirium as a possible cause of changes in the patient’s altered mental status (AMS). It is important to note that amino and organic acid test results were obtained and were not consistent with urea cycle defect.

After three additional days of using different lactulose regimens (20 g three times daily, which was later increased to a frequency of every two hours), the patient’s ammonia level was still elevated at 150 mcmol/L with worsening AMS symptoms. Rifaximin (Xifaxan, Salix Pharmaceuticals) 550 mg twice daily was added to the drug regimen to help reduce ammonia levels. Rifaximin eliminates ammonia-producing bacteria and has an off-label use in the reduction of ammonia levels in the blood and brain.

On day 10, the patient became acutely decompensated and was found to be obtunded but responsive to painful stimulus. There was no clear cause of acute decompenation, including intestinal bleeding, but the patient’s clinical state doubtless compromised his metabolic state. The patient’s mental status, which had been waxing and waning since admission, appeared noticeably deteriorated. He was progressively more somnolent with his ammonia level severely elevated (311 mcmol/L). Blood cultures, urine culture, portable chest x-ray, and arterial blood gas ordered for the patient revealed significant respiratory alkalosis leading to an admission to the medical ICU.

Lactulose was discontinued to reduce risk of diarrhea. Sustained low-efficiency dialysis was initiated to remove excess ammonia concentration but was subsequently discontinued for lack of effectiveness. As ammonia level remained elevated, sodium phenyl acetate/sodium benzoate injection (Ammonul, Valeant Pharmaceuticals) was recommended as first-line therapy. Due to formulary constraints, the rounding clinical pharmacist recommended an alternative therapy with the use of IV levocarnitine 1,000 mg every six hours for the patient’s

<table>
<thead>
<tr>
<th>Vital Signs and Laboratory Tests</th>
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<tbody>
<tr>
<td>Maximum body temperature</td>
<td>98.5°F</td>
</tr>
<tr>
<td>Blood pressure upon MICU admission</td>
<td>148/74 mm Hg</td>
</tr>
<tr>
<td>Respiratory rate upon MICU admission</td>
<td>23</td>
</tr>
<tr>
<td>Pulse</td>
<td>119</td>
</tr>
<tr>
<td>Peripheral capillary oxygen saturation pressure</td>
<td>80%</td>
</tr>
<tr>
<td>Weight</td>
<td>70.8 kg</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.5 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>7.1%</td>
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<tr>
<td>Serum sodium</td>
<td>146 mEq/L</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>3.5 mEq/L</td>
</tr>
<tr>
<td>Serum chloride</td>
<td>109 mEq/L</td>
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<tr>
<td>Serum bicarbonate</td>
<td>27 mEq/L</td>
</tr>
<tr>
<td>Serum blood urea nitrogen</td>
<td>15 mg/dL</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.0 mg/dL</td>
</tr>
<tr>
<td>White blood cells</td>
<td>16.1 × 10⁹/L</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.5 g/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>193 × 10⁹/L</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>38.7%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Imaging Test Results</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Chest x-ray (indication: shortness of breath)</td>
<td>No acute thoracic abnormality</td>
</tr>
<tr>
<td>CT scan of chest with contrast (indications: shortness of breath, hypoxia, tachycardia)</td>
<td>No CT evidence of pulmonary embolus to the segmental level; multiple lung nodules of lytic bone lesions consistent with metastatic disease; right thyroid 1.3-cm nodule, unchanged</td>
</tr>
</tbody>
</table>

CT = computed tomography; MICU = medical intensive care unit.
hyperammonemia. After the first dose of IV levocarnitine, the patient’s ammonia levels decreased, while his mental status and vital signs improved markedly.

Following treatment with IV levocarnitine for three days, the patient’s ammonia level decreased to 69 mcmol/L (Figure 1). IV levocarnitine therapy was subsequently switched to three tablets of levocarnitine 330 mg twice a day, which helped stabilize the patient. He was consequently downgraded to supportive care until vandetanib was restarted for cancer treatment.

DISCUSSION

Hyperammonemia may present with respiratory alkalosis, nausea, irritability, seizures, and lethargy progressing to coma. An elevated ammonia level is a well-established cause of hepatic encephalopathy.5 Hepatic failure, urea cycle defects, organic acidemias, and Reye’s syndrome are common causes of hyperammonemia.6 Organisms such as Proteus mirabilis can also cause infections that elevate ammonia levels.7 Other rare causes include transjugular intrahepatic portosystemic shunting, parenteral nutrition, and adverse drug effects; drugs such as valproic acid may cause ammonia levels to become elevated.8–14

High levels of ammonia arise mostly as a result of hepatic encephalopathy, which commonly occurs in patients with liver cirrhosis, and it is characterized by impaired mental function and hyperammonemia.15 Ammonia is a toxic gas generated as a byproduct of protein digestion and bacterial metabolism. Elimination of ammonia is a primary function of the liver. In situations where the liver cannot eliminate ammonia effectively from the body, elimination depends on the brain, muscles, and kidney. The brain does not have an effective urea cycle, and increased entry of ammonia to the brain may result in neurological disorders (Figure 2).16 Ammonia is detoxified by urea synthesis in the kidney. It is further released to the liver through portal circulation and converted to urea through the urea cycle.

Treatment of acute hyperammonemia includes prompt diagnosis and treatment of the pathogenesis. Clinical trials have demonstrated the effective use of lactulose and lactitol enemas in the treatment of acute hepatic encephalopathy.17,18 Nevertheless, lactulose and lactitol have significant gastrointestinal adverse effects. For patients with hyperammonemia resistant to lactulose or lactitol, neomycin, metronidazole, and rifaximin are second-line agents.19–21 Newer therapies being studied include nitazoxanide, the molecular adsorbent recirculating system, L-ornithine phenylacetate, levocarnitine, and sodium benzoate/sodium phenylacetate.22 IV sodium phenylacetate/sodium benzoate has been shown to lower ammonia levels and improve survival.23 Hemodialysis may also be needed to manage hyperammonemia in patients who do not respond to drug therapies.

In this case, all possible causes of AMS were ruled out. The amino and organic acids profile was not consistent with a urea cycle defect. The calcium level was within normal limits. Laboratory results showed no liver damage or abnormalities. The initial cause of the AMS changes was not immediately evident but was likely linked to high ammonia levels.15 Ammonia is a toxic gas generated as a byproduct of protein digestion and bacterial metabolism. Elimination of ammonia is a primary function of the liver. In situations where the liver cannot eliminate ammonia effectively from the body, elimination depends on the brain, muscles, and kidney. The brain does not have an effective urea cycle, and increased entry of ammonia to the brain may result in neurological disorders (Figure 2).16 Ammonia is detoxified by urea synthesis in the kidney. It is further released to the liver through portal circulation and converted to urea through the urea cycle.
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Figure 2 Development of Hyperammonemia

Excess ammonia in the brain causes neurotoxicity due to the lack of a urea cycle. (Credit: Jane Missler and Claudia Zwingmann)

Figure 3 Suggested Action of L-Carnitine

CPT1 = carnitine palmitoyltransferase 1; CPT2 = carnitine palmitoyltransferase 2.

L-carnitine can facilitate the entry of fatty acids into the mitochondria. These fatty acids can be used to produce energy. A) Fatty acids must first be activated in the outer mitochondrial membrane before they can be used. Acetyl-CoA synthetase activates the fatty acid and transforms it to acyl-CoA. B) Activated fatty acids in the form of acyl-CoA are carried across the mitochondrial membrane by L-carnitine. L-carnitine is recycled back. In the mitochondria, acyl-CoA undergoes β-oxidation to produce acetyl-CoA, which is used for mitochondrial energy production in the tricarboxylic acid cycle. (Credit: Jane Missler and Claudia Zwingmann)

the urea cycle via carbamyl phosphate synthetase activation. Therrien et al. showed in vitro that levocarnitine protects against ammonia neurotoxicity among patients after portacaval-shunt surgery. Levocarnitine is classified as a dietary supple-

ment and is indicated in the treatment of primary and secondary systemic carnitine deficiency. It is also used off-label in the treatment of elevated ammonia levels. A previous study had shown that levocarnitine can be used in valproic-acid–induced hyperammonia coma, and hepatic dysfunction due to valproic acid overdose/toxicity. It is suggested as a potential therapeutic agent in metabolic hepatic encephalopathies. The protective effect of L-carnitine was attributed to significant improvements in the cellular redox state and mitochondrial energy metabolism (Figure 3). Studies have demonstrated that levocarnitine is able to reduce ammonia levels (and increase energy metabolism) of which normal plasma levels range from 9 to 33 mcg/L.

At our hospital, there is a focus on providing the highest-quality health care while implementing cost-saving strategies in a setting of limited resources. At the time this patient was initially prescribed sodium phenyl acetate/sodium benzoate (Ammonul), it was disapproved due to formulary constraints. Eventually, the clinical pharmacist suggested an alternative therapy (levocarnitine). Treating this patient with levocarnitine saved the hospital more than $200,000. The average wholesale price of sodium phenyl acetate/sodium benzoate therapy adds up to $54,792.71 per 50-mL vial. In contrast, IV levocarnitine’s average wholesale price is $13.20 per 5-mL vial and $1.10 per 300-mg tablet. For five doses, the cost of levocarnitine added up to $66.00, whereas, the estimated cost of sodium phenyl acetate/sodium benzoate therapy would have been $219,170.83. Utilizing the clinical pharmacist’s suggested intervention saved our institution more than $200,000 in this case.

CONCLUSION

Although sodium phenyl acetate/sodium benzoate has been shown to be an effective treatment for hyperammonemia, the cost has limited its use in our institution. When making formulary drug decisions, effectiveness and cost are relevant factors. In this case, a significant value was obtained through the use of levocarnitine. In cases of altered mental status with no etiology, blood ammonia levels should be checked, even when there is no hepatic damage or relevant laboratory abnormality. This is especially true for cancer patients due to possible neoplastic syndrome. In cases of nonhepatic hyperammonemia-induced AMS, levocarnitine
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therapy may be very cost-effective in lowering blood ammonia levels. Furthermore, measuring carnitine levels can be useful in diagnosing unexplained AMS. It is relatively safe with few adverse effects, which may include hypertension, chest pain, headache, nausea, vomiting, and diarrhea. No renal or hepatic dosage adjustment is required, and no known significant drug interaction has been reported. Levocarnitine, though generally well tolerated, with rare adverse effects including swelling of the hands and lower extremities, and seizures, was not an initial choice because it was off-label.30,31 As always, it is necessary to evaluate risks and benefits before any drug use.

This case illustrates the pharmacist’s role in the ICU—not just in clinical terms, but in the sense that enormous economic gains were made by using levocarnitine as opposed to Ammonul.

REFERENCES


