Hepatic encephalopathy in horses, as in many mammals, has been researched for some time. Although there is little question regarding which diseases can cause hepatic encephalopathy, the mechanism of neurologic disease and, therefore, effective treatment options remain controversial. This article discusses leading theories regarding the pathogenesis of hepatic encephalopathy, current treatment modalities, and new areas of research.

CAUSE

Hepatic encephalopathy is caused by either direct damage to the liver or intestinally derived toxins that overwhelm or bypass the liver. These toxins access the central nervous system (CNS), resulting in encephalopathic signs. Hepatic encephalopathy in horses most commonly occurs secondary to hepatic insufficiency due to megalocytic hepatopathy resulting from pyrrolizidine alkaloid toxicosis caused by ingestion of plants such as Senecio (ragwort), Crotalaria (rattlebox), and Amsinckia (fiddleneck) spp. Other causes of hepatic insufficiency and hepatic encephalopathy are Theiler’s disease, Tyzzer’s disease, cholangiohepatitis, chronic active hepatitis, hepatic neoplasia, toxic hepatopathy, and portosystemic shunts. In all of these diseases and conditions, because the liver is incapacitated, it is unable to perform its normal detoxification...
activities, and gastrointestinal (GI)-derived toxins enter the CNS via the bloodstream. There is some consensus that the blood–brain barrier is compromised secondary to hepatic insufficiency.\(^5,7\) This exacerbates CNS pathology as an even greater amount of gut-derived neurotoxins enter the CNS.

Although several theories abound regarding the cause of hepatic encephalopathy, a few have remained at the forefront of research. Many of these theories may well pertain to the true nature of hepatic encephalopathy, but it is probable that they are all related and the disease is multifactorial. The following theories shape the current treatment approach.

Ammonia (NH\(_3\)) has long been considered a putative neurotoxin in the development of hepatic encephalopathy.\(^2,7,8\) Although NH\(_3\) is generally thought to contribute to the pathogenesis of hepatic encephalopathy, there is evidence that promotes and negates the associated importance of NH\(_3\). Altered amino acid (AA) metabolism with up-regulation of aromatic AAs and down-regulation of branched-chain amino acids (BCAAs) is thought to lead to direct neural inhibition secondary to the effects of aromatic AAs on the CNS. Alteration of \(\gamma\)-aminobutyric acid (GABA) and glutamate neurotransmission during liver failure is also thought to play a significant role in the pathophysiology of hepatic encephalopathy (Figure 1). It is believed that liver failure leads to an increase in endogenous benzodiazepine-like substances that effectively inhibit neural excitation. It is likely that multiple mechanisms work in synergy with each other to create encephalopathic signs.\(^2\)

### Ammonia

To understand the method by which NH\(_3\) is thought to play a role in hepatic encephalopathy and, therefore, why treatment is largely centered on reducing blood NH\(_3\) levels, clinicians must understand the normal metabolism of NH\(_3\), NH\(_3\) is generated in the body by four mechanisms:

- In the cecum and colon by urease-producing microorganisms
- Cleavage of AAs obtained from the diet
- Catabolism of glutamine by enterocytes
- Peripheral tissue (muscle) waste

Also, dietary intake of protein leads to energy generation by AA deamination in the liver. During normal hepatic metabolism, once NH\(_3\) reaches the bloodstream, it has one of two fates. In the event that the detoxification capacity of the liver is overwhelmed, azotemia ensues; NH\(_3\) crosses the blood–brain barrier; and the CNS, lacking an effective urea cycle, detoxifies NH\(_3\) to glutamine.\(^4,7,9\) CNS astrocytes are responsible for this detoxification.\(^9\) The transport of NH\(_3\) across the blood–brain barrier is enhanced by structural changes in the blood–brain barrier secondary to hyperammonemia,\(^4\) although the importance of this effect is controversial.\(^2\) NH\(_3\) is thought to alter cerebral blood flow,\(^1,2,5\) affect electrophysiologic properties in the CNS, interfere with normal neurotransmission, and damage CNS astrocytes, leading to formation of Alzheimer’s type II cells and neural degeneration.\(^4,7,9\) Because elevated glucagon levels have been shown to exist in dogs and rats with hepatic insufficiency, it is possible that increased hepatic gluconeogenesis from AAs ensues, further elevating systemic NH\(_3\) levels.\(^7\)

Several studies\(^1,2,5\) support the role of NH\(_3\) as a putative neurotoxin in the development of hepatic encephalopathy.\(^2,7,8\) Although NH\(_3\) is generally thought to contribute to the pathogenesis of hepatic encephalopathy, there is evidence that promotes and negates the associated importance of NH\(_3\). Altered amino acid (AA) metabolism with up-regulation of aromatic AAs and down-regulation of branched-chain amino acids (BCAAs) is thought to lead to direct neural inhibition secondary to the effects of aromatic AAs on the CNS. Alteration of \(\gamma\)-aminobutyric acid (GABA) and glutamate neurotransmitter function.
neurotoxin. Encephalopathy can be induced in cirrhotic patients via \( \text{NH}_3 \) administration. Other research has found that congenital hyperammonemia results in encephalopathy in dogs and children. Also, therapeutic reduction of GI \( \text{NH}_3 \) has resulted in improvement in horses, dogs, and humans with hepatic encephalopathy. Furthermore, cerebrospinal fluid (CSF) glutamine concentrations correlate with the degree of encephalopathy in humans. In humans and horses, \( \text{NH}_3 \)-lowering drugs improve clinical signs associated with hepatic encephalopathy.\(^5\) In horses, hyperammonemia has been linked to encephalopathic clinical signs without evidence of liver disease, leading to formation of Alzheimer II cells.\(^1,5,10\) This suggests that, in horses, hyperammonemia alone may cause hepatic encephalopathy.

However, other studies\(^1,8,11\) show that \( \text{NH}_3 \) concentrations do not correlate with the severity of hepatic encephalopathy or CNS histopathology, although the severity of liver disease does correlate.\(^1\) Also, electroencephalograms (EEGs) following infusion of \( \text{NH}_3 \) in normal animals do not match EEGs in animals with hepatic encephalopathy,\(^2\) suggesting that hepatic encephalopathy is multifactorial. Furthermore, some patients may have encephalopathy despite normal blood \( \text{NH}_3 \) levels.\(^4\) One study\(^2\) showed that treatment with \( \text{NH}_3 \)-lowering monoamine oxidase inhibitors did not improve clinical signs of hepatic encephalopathy. Another study\(^2\) showed that artificially injecting \( \text{NH}_3 \) into horses did not elicit clinical signs consistent with naturally occurring hepatic encephalopathy. Bromocriptine seems to lessen signs of hepatic encephalopathy while blood \( \text{NH}_3 \) levels remain unchanged, also suggesting a multifactorial pathophysiology.\(^2,4,7\)

**Altered Amino Acid Metabolism**

Alteration of monoamine neurotransmitter synthesis is widely believed to be an important factor in the pathogenesis of hepatic encephalopathy.\(^2,3,7,12\) During liver failure, altered muscle catabolism decreases plasma BCAAs such as valine, leucine, and isoleucine. Simultaneously, in patients with hepatic insufficiency, the liver fails to metabolize aromatic AAs such as phenylalanine, tyrosine, and tryptophan (Figure 2). The combination of these events creates elevated systemic—and, therefore, CNS aromatic—AA levels, which is thought to lead to several events, including synthesis of false neurotransmitters, reduction of stimulatory neurotransmitters, and synthesis of inhibitory neurotransmitters.\(^2,3,6,11,13,14\)

Furthermore, CNS influx of aromatic AAs leads to intraneuronal efflux via a cell wall exchange transport process. The net effect of altered AA metabolism is twofold:

- Down-regulation of excitatory neurotransmitters and an increase in false neurotransmitters displace normal neurotransmitters from the synaptosomes of presynaptic nerve endings.\(^7\)
- Enhanced production of inhibitory neurotransmitters leads to reduced neuronal excitation and increased neuronal inhibition

Both effects result in CNS depression.

**Altered GABA and Glutamate Transmission**

Clinical signs (see section on p. 164) in horses with hepatic encephalopathy are consistent with both excitatory and inhibitory neural activity. Therefore, glutamate and GABA, the major known excitatory and inhibitory neurotransmitters, respectively, are believed to play a key role in the pathogenesis of hepatic encephalopathy.\(^2,13\) Alteration in GABA neurotransmission begins with an influx of GI-derived GABA and a decreased rate of hepatic extraction of GABA.\(^7\) Although GABA normally
cannot effectively penetrate the blood–brain barrier, some patients with hepatic encephalopathy may have a damaged blood–brain barrier, allowing GABA to enter in larger amounts.

Simultaneously, “supersensitivity” to GABA is created by NH$_3$, mercaptans, and short-chain fatty acids, which reach the CNS via the intestinal tract. These toxins also interfere with the ability of the brain to detoxify NH$_3$. These toxins may be present in the CNS because a damaged or diseased liver cannot properly transform or convert these monomers. Research has shown that CNS GABA concentrations correlate with the grade of recognized encephalopathy. GABA itself increases CNS GABA receptors and decreases CNS glutamine receptors. In rats and rabbits with experimentally induced hepatic encephalopathy secondary to fulminant liver failure, increased CNS GABA receptors were present. Although the direct cause of this remains unknown, it supports the theory that GABA plays a key role in hepatic encephalopathy.

Furthermore, both GABA and glutamate are thought to be central to the cerebral glutamate system, in which an intimate interrelationship exists between GABA and glutamate wherein fluctuations in one neurotransmitter are compensated for by fluctuations in the other. NH$_3$ is crucial in regulating this relationship. Hepatic encephalopathy may be associated with increased sensitivity to inhibitory AA neurotransmitters.

**Increase in Endogenous Benzodiazepine-like Substances**

Studies show that rabbits and humans with hepatic encephalopathy have increased benzodiazepine-like compounds in their serum and CNS. These compounds are believed to be intestinal in origin. The GABA receptor can be synergistically stimulated by GABA, benzodiazepines, and barbiturates, leading to neural inhibition and clinical signs of depression. Research has shown that drugs that counter the effects of benzodiazepines (flumazenil) and barbiturates (naloxone) in animals with hepatic encephalopathy can ameliorate clinical signs of the disease.

The benzodiazepine-like GABA effect is enhanced in patients with hepatic encephalopathy by increased availability of GABA-receptor agonists, increased density or affinity of GABA receptors, and allosteric potentiation of GABA action at the level of the receptor. This allosteric potentiation has been evidenced in studies in which benzodiazepine antagonists were administered to animals and humans with hepatic encephalopathy. These patients experienced transient improvement in their neurologic status.

**HISTOPATHOLOGY**

The classic appearance of CNS tissue from horses with hepatic encephalopathy and insufficiency involves...
the presence of Alzheimer type II cells, which are astrocytes (support cells) with characteristic clear, swollen vesicular astrocyte nuclei in gray matter\(^4\)\(^,\)\(^7\) (Figures 3 and 4). Formation of Alzheimer type II cells is thought to occur when CNS astrocytes, lacking an effective urea cycle, metabolize NH\(_3\) to make glutamine. However, at high concentrations, glutamine can be neurotoxic. One study\(^1\)\(^1\) showed that horses with signs of hepatic encephalopathy had lost approximately 50% to 60% of liver function. This is in contrast to other reports\(^3\)\(^,\)\(^13\) stating that the equine liver has an 80% reserve and that at least that much liver must be damaged before the onset of hepatic insufficiency. In cases of pyrrolizidine toxicosis, hepatocyte megalocytosis is common.\(^1\)\(^1\)

Although some researchers believe that a disparity exists between the severity of clinical signs and the histopathologic changes in the CNS,\(^4\) others claim that tissue changes are commonly detected via necropsy in horses with hepatic encephalopathy and hepatic insufficiency.\(^10\)\(^,\)\(^12\) The mechanism of Alzheimer type II cells is thought to be due to the osmotic effects of increased intracellular astrocytic glutamine concentrations.

Researchers have found that the basal nuclei (basal ganglia) are commonly affected in horses with hepatic encephalopathy.\(^4\) The basal nuclei are implicated in Parkinson’s disease and lie within the M1 corticomuscular region of the neocortex.\(^17\) A subset of neurologic disorders occurring in humans and horses with hepatic encephalopathy includes irregular, jerky lapses of posture that are almost rhythmic (this is called “mini-asterixis” in humans). This condition has a clear correlation to Parkinson’s disease, in which the basal nuclei are primarily affected. Therefore, pathologic basal nuclei tissue in horses with hepatic encephalopathy and hepatic insufficiency may have a causal role in the clinical signs in horses with hepatic encephalopathy.

**No specific clinical feature distinguishes hepatic encephalopathy from other CNS disorders.**

**CLINICAL PRESENTATION**

The clinical presentation of hepatic encephalopathy in horses is commonly categorized into four numeric divisions\(^1\)\(^–\)\(^3\),\(^5\)\(^–\)\(^7\),\(^11\),\(^13\) (see box on this page). Stage I is the first and most mild form of hepatic encephalopathy. At this stage, gut-derived toxicants are just beginning to affect the CNS. Horses may show signs of mild confusion, inappetence, dull demeanor, or mild irritability. “Personality” changes begin to manifest, and the owner or trainer is the best source of information regarding these changes. One of the most obvious clinical signs to the veterinarian is general disorientation of the horse. By stage III of hepatic encephalopathy, the horse is obviously uncoordinated, somnolent, very confused in its surroundings, and occasionally aggressive toward the owner and veterinarian. Seizure is another clinical sign of a stage III hepatoencephalopathic horse. This is the stage in which examination and treatment of patients with hepatic encephalopathy is most dangerous. Yawning can be observed at stages I, II, or III. Stage IV is marked by recumbence, unarousable somnolence, and coma and eventually leads to death. Unfortunately, none of these stages is distinguishable from other neurologic pathologies. Therefore, it is crucial to document changes...
in liver enzymes in addition to clinical signs to make a diagnosis of hepatic encephalopathy.

Jaundice or photosensitization may be found at any stage, although in one study, only 42% of horses with hepatic insufficiency had jaundice. If hepatic encephalopathy is due to hepatic insufficiency caused by portosystemic shunts in foals, patients may be younger than 12 months of age, small for their age, and in poor condition.

**DIAGNOSIS**

Diagnosis of hepatic encephalopathy is based on the presence of neurologic clinical signs found in conjunction with physical examination and laboratory findings documenting liver disease. Common serum chemistry laboratory abnormalities found in horses with hepatic encephalopathy include hyperammonemia; elevated serum bile acid, \( \gamma \)-glutamyltransferase (GGT), aspartate aminotransferase, and sorbitol dehydrogenase levels; and elevated sulfobromophthalein clearance. Elevated GGT levels are proportionately associated with higher mortality. Because NH\(_3\) levels vary according to NH\(_3\) production and metabolism, NH\(_3\) is not a good indicator of disease but rather a means of monitoring the patient’s clinical status. Surprisingly, only about 50% of horses with primary hepatic disease exhibit clinical signs of hepatic encephalopathy. Results of CSF analysis are usually normal.

The differential diagnosis should include all causes of hepatic encephalopathy and insufficiency (as already discussed in the section on cause) as well as rabies, West Nile virus, granulomatous meningoencephalitis, equine protozoal myelitis, leukoencephalomalacia, Eastern equine encephalomyelitis, Venezuelan equine encephalomyelitis, Western equine encephalomyelitis, neoplasia, and aberrant parasite migration.

Hepatic encephalopathy can be accompanied by bilateral
Hepatic Encephalopathy

General laryngeal paralysis and gastric impaction. These signs are always associated with a poor prognosis for survival. The mechanism of action for these clinical signs is speculative. Although electroencephalography is not currently applicable in horses, it can be used to detect hepatic encephalopathy in humans. Monitoring the generation of visual evoked potentials, which can be objectively measured and can represent postsynaptic neuronal activity evoked by a visual afferent stimulus, leading to a distinctive, specific, and measurable pattern, is also applicable only in humans with hepatic encephalopathy.

THERAPY

The major principle in treating horses with hepatic encephalopathy is to support the patient until the liver regenerates. This involves sparing the liver from as many of its normal homeostatic functions as possible. To begin, source elimination is essential. Depending on the underlying disease, this may involve binding a toxin, treating a liver-specific infectious agent, or correcting a metabolic disturbance. Horses in stages II and III are generally atactic and potentially dangerous or aggressive; chemical restraint can prevent self-inflicted trauma to the horse and make veterinary support easier and safer. When horses with hepatic encephalopathy are sedated, it is important to decrease all drug doses because most sedatives are eliminated via the liver. Clinicians should avoid the use of diazepam because it can bind to the GABA receptor and potentiate its neuroinhibitory effects.

Intravenous fluids are recommended to enhance dilution and excretion of neurotoxic substances; support central venous pressure, thereby preventing further lactic acidosis; and enhance electrolyte homeostasis because affected animals may be anorectic. It is recommended to avoid the use of fluids containing lactate (i.e., lactated Ringer’s solution) because the liver must work to eliminate that molecule from the body. Dextrose (2.5% to 10% infusion) should be added to fluids as a means of decreasing the amount of glycogenolysis and gluconeogenesis that the liver has to accomplish. Also, acid–base abnormalities, which are common in patients with hepatic encephalopathy, should be corrected.

Decrease the Ammonia Concentration

In horses with hepatic encephalopathy and hyperammonemia, clinicians should attempt to decrease the blood NH₃ concentration as much as possible. This can be accomplished by both decreasing the amount of NH₃-producing bacteria from the GI system (neomycin [30 mg/kg PO q6h] or metronidazole [15 mg/kg PO q6h]) and trapping NH₃ in the colon. However, one group claims that treatment of hepatic encephalopathy with neomycin is ineffective. Oral or rectal lactulose (333 mg/kg) aids in acidifying the colon and thus protonating NH₃ to become the cation ammonium, which cannot freely diffuse past the intestinal mucosae.

Correct Aromatic Amino Acid and Branched-Chain Amino Acid Abnormalities

Diet is the most effective means of decreasing the amount of serum and CNS aromatic AAs and increasing the level of BCAAs (see box on this page). Feeds such as beet pulp, sorghum, bran, and milo are rich in BCAAs. Feeding readily digestible carbohydrates such as cracked corn assists the liver by sparing it gluconeogenesis and glycogenolysis activity. Protein concentrations should be limited because excessive amounts of AAs are used for energy through transamination and subsequently increase the plasma NH₃ level.

In creating a diet for hepatoencephalopathic patients, it is important to have a feed that is rich in carbohydrates, low in protein, and rich in BCAAs. Frequentfeedings help maintain constant blood glucose levels, thereby sparing the liver the extra work of gluconeogenesis. Because this ration is not very palatable, it is important to remember that getting the patient to eat something is better than it not eating at all. Anorectic

Only 50% of horses with hepatic insufficiency show clinical signs of hepatic encephalopathy.
horses have elevated glucagon blood levels, leading to enhanced demand on the liver because of gluconeogenesis from AAs. This process leads to production of higher blood NH₃ levels. Glucagon also enhances hepatic glycogenolysis, further stressing the diseased liver. Therefore, molasses should be mixed into the feed. If the horse remains inappetent, a more palatable feed should be introduced between grazing intervals.

**CURRENT RESEARCH IN LABORATORY ANIMALS**

Interesting new studies on brain edema with liver failure show that on a genetic level, rats suffering from CNS hyperammonemia undergo an alteration of gene expression that codes for proteins involved in the maintenance of cell volume and neurotransmission. One study found that animals with hepatic encephalopathy lost the expression of glutamate 1 (an astrocytic glutamate transporter), resulting in increased extracellular astrocyte glutamate. This glutamate increase is thought to directly contribute to cerebral swelling due to osmotic effects. Furthermore, NH₃ causes increases in intracellular astrocytic glutamate concentrations, which may be the direct cause of Alzheimer type II cells. Animals with experimentally induced liver failure also showed posttranslational modifications of serotonin. This leads to an increased CNS concentration of serotonin, which is an important inhibitory neurotransmitter.

Other research in rats has shown that experimentally induced CNS hyperammonemia results in a loss of mitochondrial permeability transition, which is an indicator of mitochondrial energetics. Neuronal mitochondrial permeability transition increased in these animals because of a loss of protons, ions, and solutes. This leads to a loss of electron chain transport and cessation of ATP synthesis. This transition occurs in astrocytes alone and does not appear to affect neurons. This may contribute to the disease in swollen Alzheimer type II cells.

**FUTURE THERAPY**

Future therapy of horses with hepatic encephalopathy may include some of the following approaches in addition to current therapeutic modalities. Benzodiazepine receptor antagonists, although expensive, may be useful, particularly in neonatal patients. Because benzodiazepine-like substances are thought to play an important role in the course of hepatic encephalopathy (acting on the GABA
Mild hypothermia has been proven effective in attenuating the effects of brain damage and neurotrauma. In rats, mild hypothermia seems to increase the time of onset of hepatic encephalopathy and to decrease the CSF NH$_3$ concentration. The condition also appears to decrease extracellular glutamate concentrations, further preventing cerebral swelling.

L-Ornithine–L-aspartate therapy may also eventually be used in veterinary medicine (Figure 5). One study showed that in rats with experimentally induced liver failure, L-ornithine–L-aspartate therapy prevented brain edema and lowered the plasma NH$_3$ concentration. The NH$_3$-lowering effect may have been due to an observed posttranslational increase in muscle glutamine synthetase, which stimulated myotic removal of NH$_3$.

A polyherbal compound, HD-03, may also eventually play a role in treating veterinary patients with hepatic encephalopathy. One study showed that increases in aspartate aminotransferase, alanine transaminase, and NH$_3$ levels that typically occur in experimentally induced liver failure did not occur in rats pretreated with HD-03. Furthermore, gait abnormalities and/or hindlimb ataxia that typically occurs in rats induced with hepatic encephalopathy was not observed in rats pretreated with HD-03. These findings were corroborated by histologic evaluation of brain and liver tissue, which showed a protective effect in rats pretreated with HD-03.

**SUMMARY**

Because hepatic encephalopathy is a nonspecific neurologic condition that occurs as a secondary complication of primary hepatic insufficiency, the prognosis is based on the cause of the primary liver disease. However, in horses that survive hepatic encephalopathy following appropriate medical attention for their liver disease, GGT levels are usually below 250 IU/L. Furthermore, increased mortality is associated with the presence of bilateral laryngeal paralysis or gastric impaction.

The pathogenesis of hepatic encephalopathy is probably multifactorial and synergistic. The diagnosis can be made with commonly available tools, such as a clinical and/or neurologic examination as well as a routine serum chemistry profile with emphasis on GGT. Therapy should be based on lowering plasma NH$_3$ and aromatic AA levels while supporting the liver. Because there is vast ongoing research on hepatic encephalopathy, new theories and treatment options are frequently unveiled.
**REFERENCES**


**ARTICLE #1 CE TEST**

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1. What percentage of horses with hepatic insufficiency show clinical signs of hepatic encephalopathy?
   a. 5%    b. 20%    c. 50%    d. 80%    e. 100%

2. Which best represent(s) the most likely pathophysiology of hepatic encephalopathy?
   a. NH₃ is the primary cause of hepatic encephalopathy.
   b. alteration of BCAA and aromatic AA metabolism
   c. benzodiazepine-like substances
   d. alteration in GABA and glutamate transmission
   e. all of the above
3. Which is not an example of NH₃ production by horses?
   a. peripheral muscle tissue waste from normal metabolism
   b. catabolism of glutamine by enterocytes
   c. cecum production by urease-producing microorganisms
   d. cleavage of dietary AAs in the liver
   e. none of the above

4. In horses with hepatic insufficiency, tryptophan (an aromatic AA) is not metabolized by the liver and is therefore transported to the CNS, where it is converted into
   a. octopamine, a false neurotransmitter.
   b. serotonin, a neuroinhibitory substance.
   c. dopamine, a true neurotransmitter.
   d. phenylethanolamine, a false neurotransmitter.
   e. tyrosine, another aromatic AA.

5. Which statement regarding the clinical signs of hepatic encephalopathy is incorrect?
   a. The clinical signs are often unnoticed in the early stages.
   b. Because of the sudden onset of clinical signs, they are unique compared with those of other neurologic diseases.
   c. The clinical signs are indistinguishable from those of other neurologic diseases.
   d. The clinical signs are usually accompanied by increased serum GGT concentrations.
   e. The clinical signs may include disorientation and aggressive behavior.

6. Which laboratory value, if significantly elevated, most accurately correlates with mortality in horses with hepatic insufficiency?
   a. antidiuretic hormone
   b. aspartate transaminase
   c. alkaline phosphatase
   d. GGT
   e. total bilirubin

7. In treating horses with signs of hepatic encephalopathy, the primary goal is to
   a. remove all GABA-like substances from the systemic circulation.
   b. increase the BCAA:aromatic AA serum concentration ratio.
   c. support the liver until it regenerates.
   d. remove the liver toxicant (when applicable).
   e. c and d

8. If chemical restraint is necessary when treating a horse with clinical signs of hepatic encephalopathy, it is important not to administer diazepam because it
   a. is likely to induce an anaphylactic reaction.
   b. causes extreme aggressiveness in horses.
   c. enhances signs of hepatic encephalopathy by binding to GABA receptors.
   d. enhances signs of hepatic encephalopathy by binding to opioid receptors.
   e. binds to α₂-systemic receptors, causing vasoconstriction and cardiovascular shock.

9. Administration of flumazenil might help patients showing signs of hepatic encephalopathy because the drug
   a. suppresses the effect of barbiturates.
   b. is a benzodiazepine receptor antagonist.
   c. competitively binds to systemic aromatic AAs.
   d. is a GABA receptor antagonist.
   e. enhances conversion of dopamine to serotonin.

10. L-Ornithine–L-aspartate therapy may be effective in treating hepatic encephalopathy because the combination
    a. enhances NH₃ removal from the bloodstream.
    b. reduces gut-derived GABA-like molecules.
    c. directly reduces brain edema.
    d. decreases endogenous serotonin.
    e. a and c