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Review Article

Anticonvulsants in Hepatic Encephalopathy

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Abstract

Hepatic encephalopathy (HE) is a complex neurological syndrome that arises as a complication of liver dysfunction. The primary focus in HE management has traditionally been on ammonia detoxification, but recent research has paved light on the potential role of anticonvulsant medications in improving the cognitive impairment and preventing seizures associated with HE. This review mainly aims to provide a comprehensive analysis of the use of anticonvulsants in hepatic encephalopathy, by taking a looking at their mechanisms of action, efficacy, and safety profiles.

Keywords: Hepatic encephalopathy, Anticonvulsants, Cognitive impairment

Introduction:

Hepatic encephalopathy is a reversible decrease in neurological function caused by liver disease. The cognitive dysfunction associated with HE significantly impacts the quality of life of affected individuals. While ammonia remains a key player in the pathogenesis, recent studies have suggested that neuroinflammation and oxidative stress contribute to the neurological manifestations of HE. ¹ Anticonvulsants, known for their neuroprotective properties, have emerged as potential therapeutic agents in the management of HE. Psychiatric disturbances manifest as agitation, personality change, delusions, etc. Aims of seizure management include treatment of basic disease, correction of precipitant factors, imaging of head, and choice of a pharmacologically safe agent. The absolute data for safety profile of drugs in liver disease is still not clear, as changes in the pharmacokinetic data make choice of drugs difficult. Free drug concentrations may be higher, making plasma concentration monitoring essential in such situations. A single seizure may not require any therapy. However, when started, antiepileptic drugs are usually discontinued early. Drugs with sedative effects are best avoided because of a risk of precipitating coma. Phenytoin and gabapentin are relatively preferred drugs and monitoring of drug levels is desirable. Management of agitation includes physical restraint and medication. Benzodiazepines are best avoided. Haloperidol is a safer choice in the presence of liver disease. Overall management of neuropsychiatric state mainly aims at management of underlying pathology, the intent of

which leads to improvement in the clinical features of hepatic encephalopathy. ²

Causes:

The primary cause of hepatic encephalopathy is the accumulation of toxins, particularly ammonia, in the brain due to impaired liver function. The liver plays a major role in detoxifying substances absorbed from the gastrointestinal tract, and when it fails, harmful substances can accumulate and affect the central nervous system. ²

1. Cirrhosis is the most common cause of hepatic encephalopathy. It represents the advanced scarring of the liver tissue due to long-term liver damage caused by conditions such as chronic viral hepatitis (B, C), alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and autoimmune liver diseases.

2. Sudden and severe liver dysfunction, as seen in acute liver failure, hepatic encephalopathy can develop rapidly.

3. Portal hypertension, is often associated with advanced liver disease. This can lead to the diverting of blood away from the liver, bypassing its detoxification functions and allowing toxins to reach the systemic circulation and the brain.

4. Gastrointestinal bleeding, commonly associated with conditions like oesophageal varices, can result in the release of blood and its breakdown products into the digestive tract.

5. Infections, particularly bacterial infections in the gut, can lead to an increase in ammonia production.

6. Reduced blood volume and dehydration can worsen hepatic encephalopathy by concentrating toxins in the blood and impairing kidney function.

7. Imbalances in electrolytes, such as potassium and sodium, can contribute to the development or worsening of hepatic encephalopathy.

8. Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure used to treat complications of portal hypertension, it can sometimes lead to or provoke hepatic encephalopathy.

9. Inherited metabolic disorders affecting the liver's ability to process toxins can contribute to hepatic encephalopathy.

Mechanism of action of anticonvulsants:

Anticonvulsants, also known as antiepileptic drugs (AEDs), exert their therapeutic effects by regulating various physiological processes in the brain to reduce or prevent abnormal electrical activity associated with seizures.

Many anticonvulsants enhance the inhibitory effects of gamma-aminobutyric acid (GABA), which has a major inhibitory neurotransmitter in the brain. Drugs like benzodiazepines (e.g., diazepam, lorazepam) and barbiturates (e.g., phenobarbital) increase the frequency of GABA-mediated chloride channel opening, and leading to increased inhibitory synaptic transmission. Sodium channels also play a crucial role in the initiation and propagation of action potentials. Anticonvulsants like phenytoin, carbamazepine, and lamotrigine act by inhibiting voltage-gated sodium channels, reducing the excitability of neurons and prevent the spread of abnormal electrical activity. Calcium channels are mainly involved in neurotransmitter release and neuronal excitability. Some of the anticonvulsants, such as gabapentin and pregabalin, can modulate calcium channels, thus reducing the release of excitatory neurotransmitters and reducing neuronal hyperactivity. While Levetiracetam is believed to modulate neurotransmitter release by binding to synaptic vesicle protein 2A (SV2A).³

Anticonvulsants in Hepatic Encephalopathy:

Anticonvulsants are not typically the first-line treatment of choice for hepatic encephalopathy, but they may be used in certain cases, especially when seizures are present or as part of a broader management strategy.

- A. **Valproic Acid:** Valproic acid is an anticonvulsant with potential neuroprotective properties. In the context of hepatic encephalopathy, particularly its ability to modulate neurotransmitter release and exert anti-inflammatory effects. The use of valproic acid in liver disease requires careful monitoring, as it may potentially cause hepatotoxicity in the patients.³
- B. **Levetiracetam:** Levetiracetam is an anticonvulsant that has a wide range for its potential neuroprotective effects in hepatic encephalopathy. Levetiracetam is generally well-tolerated, and its use in liver disease does not pose significant concerns regarding hepatic metabolism.⁴
- C. **Gabapentin:** Gabapentin, is another anticonvulsant, which has been investigated in the management of hepatic encephalopathy. Its mechanism of action involves regulation of calcium channels, and it has the ability to reduce the frequency and severity of hepatic encephalopathy episodes. Like levetiracetam, gabapentin is generally well-tolerated, but individual patient factors should be considered.

It's important to note that while anticonvulsants may have potential benefits in hepatic encephalopathy, the primary treatment for this condition often involves the treatment of the underlying liver dysfunction and using medications like lactulose or rifaximin to reduce ammonia levels in the body. The choice of anticonvulsant, if considered, would depend on factors such as the patient's overall health, the presence of seizures, and the potential for drug interactions.

Neuroprotective Effects of Anticonvulsants in Hepatic Encephalopathy:

Hepatic encephalopathy (HE) is an alarming challenge in the area of hepatology, where there is an intricate interplay between liver dysfunction and neurological manifestations which necessitates innovative therapeutic approaches in the field of hepatology.

1. Anticonvulsants, such as valproic acid and levetiracetam, exert their neuroprotective effects through regulating of neurotransmitter systems. The enhancement of gamma-aminobutyric acid (GABA)ergic inhibition and the modulation of glutamate receptors contribute to the stabilization of neuronal excitability, potentially reducing neurotoxicity in HE.

2. Some anticonvulsants exhibit anti-inflammatory properties that extend above their primary antiseizure mechanisms. The suppression of neuroinflammatory responses has a major role in protecting neurons from the harmful effects of increased ammonia levels which is a characteristic of hepatic encephalopathy.

3. Excitotoxicity, arising from the excessive release of excitatory neurotransmitters, is involved in the pathogenesis of HE. Anticonvulsants, including gabapentin, by modulating calcium channels and inhibiting glutamate release, may contribute to preventing excitotoxic neuronal damage.

4. Anticonvulsants may also enhance neuronal support in the face of metabolic and toxic insults associated with hepatic encephalopathy.⁵

Efficacy studies:

Efficacy studies play a crucial role in evaluating the effectiveness of anticonvulsants in the management of hepatic encephalopathy (HE).

Valproic acid appears to be effective in managing hepatic encephalopathy, with a notable impact on both the frequency of episodes and cognitive outcomes. Gabapentin on the other hand is found to be effective in managing hepatic encephalopathy symptoms, with potential benefits in reducing severity and improving cognitive outcomes. Valproic acid shows a long-term therapeutic option for individuals prone to recurrent hepatic encephalopathy episodes and also have a positive impact on neurocognitive outcomes in patients with hepatic encephalopathy, highlighting its potential neuroprotective effects.

Levetiracetam shows its efficacy in both seizure control and cognitive improvement in patients with hepatic encephalopathy. Cognitive improvements were also seen, supporting the potential use of levetiracetam in managing neurological symptoms associated with hepatic encephalopathy. Levetiracetam has its efficacy in seizure control and cognitive improvement, suggesting its role as a better treatment option for hepatic encephalopathy.⁶

Safety concerns:

The safety use of anticonvulsants in hepatic encephalopathy (HE) is an important aspect to consider, especially given the potential impact on liver function and the overall well-being of

individuals with liver disease. It's essential to evaluate each and every anticonvulsant medication individually, as their safety profiles can vary from one drug to the other. Hepatotoxicity is a main concern with certain anticonvulsants. Regular monitoring of liver function, including monitoring of liver enzyme levels, is an essential way to detect any signs of liver injury. Anticonvulsants can interact with other medications, potentially affecting their efficacy or safety. Clinicians should be aware of potential drug interactions, mainly in individuals or patients with liver disease who are likely to take multiple medications. The safety of anticonvulsants can be influenced by individual patient factors, including the severity of liver disease, the presence of comorbid conditions, and the overall health of the patient. Close monitoring of patients receiving anticonvulsants for hepatic encephalopathy is essential. This includes regular monitoring of liver function, clinical evaluation for signs of adverse effects, and adjustments of the treatment plan as needed. In some cases, alternative therapies with more favourable safety profile may be considered. ⁷

Conclusion:

Hepatic encephalopathy (HE) is a complex and multifaceted manifestation of liver dysfunction, which requires a varying therapeutic approach. This review has been into the utilization of anticonvulsants in the management of hepatic encephalopathy, understanding their causes, mechanisms of action, efficacy studies, potential neuroprotective effects, safety profiles. The analysing of anticonvulsants, including valproic acid, levetiracetam, and gabapentin, has revealed promising insights into their role in enhancing the neurological consequences associated with hepatic encephalopathy. Studies have suggested benefits of anticonvulsants in seizure management, cognitive function improvement, and a potential reduction in the frequency and severity of encephalopathy episodes.

The safety considerations of anticonvulsants in the context of hepatic encephalopathy have the importance of individualized treatment plans. Hepatotoxicity, drug interactions, are the unique challenges posed by compromised liver function necessitate combined monitoring and thoughtful selection of medications. As the field advances, the emerging therapies and ongoing research initiatives to enhance our understanding of anticonvulsant efficacy and safety in hepatic encephalopathy. The identification of these novel agents and the clarification of existing guidelines are essential steps toward optimizing patient outcomes.

In conclusion, while anticonvulsants provide a promising path for addressing certain aspects of hepatic encephalopathy, the complexities of this condition necessitate a comprehensive and patient-centred approach. As we go through the complex concept of liver-brain interactions, further research endeavours and clinical approach will undoubtedly shape the evolving role of anticonvulsants in the complete care of individuals who are affected by hepatic encephalopathy. The journey continues, to

the advancing knowledge, improving therapeutic strategies, and improving the lives of those who are struggling with the challenges of hepatic encephalopathy.

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