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REVIEWS

Should Mannitol be Administered Orally and Intravenously in Hepatic Encephalopathy?

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Abstract

Hepatic encephalopathy (HE) is a major neuropsychiatric complication in patients with liver diseases, significantly impacting survival rates and imposing substantial economic burdens. The severity of HE can be reduced and treated through the enteral and parenteral administration of mannitol, which acts on two important pathophysiological pathways: decreasing plasma ammonia levels and reducing cerebral edema.

Keywords: mannitol, hepatic encephalopathy (HE).

Rezumat

Encefalopatia hepatică este o complicație neuropsihiatrică majoră a bolnavilor cu boli de ficat cu implicații importante asupra supraviețuirii dar și cu un impact economic substanțial. Poate fi redusă și tratată gravitatea acesteia prin administrarea enterală și parenterală a manitolului care acționează pe două dintre căile fiziopatologice importante: scăderea amoniacului plasmatic și reducerea edemului cerebral.

Cuvinte cheie: mannitol, encefalopatie hepatică (EH).

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INTRODUCTION

Two of the pathophysiological mechanisms leading to the onset of hepatic encephalopathy include increased serum ammonia levels and the reduction of cerebral glutamic acid, along with the accumulation of glutamine in astrocytes, resulting in their edema. Imaging techniques (MRI and CT) support this, revealing atrophic changes and cerebral edema in hepatic encephalopathy. Some researchers argue that HE is a disorder of astrocyte function. Astrocytes are large cells of the central nervous system that control the chemical environment around neurons. They are connected by gap junctions, forming a functional syncytium. They represent one-third of cortical volume. They play a key role in controlling the blood-brain barrier and detoxifying various chemicals, including ammonia.

In cirrhosis, astrocytes may undergo significant conformational changes, leading to swelling, which macroscopically results in cerebral edema, increased intracranial pressure, and potential cerebral herniation[1].

Paraclinical Diagnostic Elements in Hepatic Encephalopathy (HE)

Hyperammonemia in venous blood. Measuring venous ammonia levels can be useful when liver pathology has not been confirmed and in the absence of other causes of altered consciousness. Elevated plasma ammonia levels are found in over 80% of patients with HE. However, ammonia levels do not have prognostic value in these patients.

Cerebral imaging methods are used for differential diagnosis to distinguish HE from cerebrovascular pathology or space-occupying lesions. In HE, cerebral computed tomography (CT) always shows generalized or localized cerebral edema and a degree of cerebral atrophy, even in well-compensated cirrhosis. Magnetic Resonance Imaging (MRI) is superior to cerebral CT in detecting the water content of brain tissue[2].

Incidence

Hepatic encephalopathy (HE) is a major complication in patients with acute or chronic liver diseases, with substantial economic impact. Manifest HE occurs in approximately 30-45% of patients with cirrhosis, while minimal HE affects up to 60% of patients with chronic liver diseases and 80% of those with cirrhosis[3]. Approximately 64% of patients admitted to intensive care units have HE as a major complication[4].

Current Therapeutic Methods

Management of HE includes identifying precipitating factors, limiting the consumption of animal proteins, and medical therapies, including:

- Lactulose (non-absorbable disaccharide) is considered the first-line treatment.
- Neomycin, Metronidazole, Vancomycin are used as alternatives for patients intolerant to or unresponsive to lactulose. These are not first-line due to their adverse effects.
- Rifaximin is a broad-spectrum antibiotic, well tolerated and frequently used in HE treatment, with effects comparable to lactulose.
- Alternative therapies that include the administration of branched-chain amino acids, ornithine-aspartate, zinc supplements, sodium benzoate, dopamine receptor agonists, benzodiazepine receptor antagonists, acarbose, and probiotics.

Current pharmacotherapy is limited compared to the complex pathophysiology of hepatic encephalopathy[5].

What We Know About Mannitol

Mannitol is classified as a prebiotic and is widely used as a food sweetener and in the cosmetics industry.

It increases plasma osmolarity, drawing water from tissues (including the brain, cerebrospinal fluid, and eyes) into the interstitial fluid and plasma.

Due to its hyperosmolar intravascular effect, mannitol has been used to treat migraines, intraocular or intracranial hypertension, ischemia/reperfusion renal injuries, Parkinson's disease, and cystic fibrosis.

When administered orally, it promotes digestive and urinary excretion of toxins or prepares the colon for functional explorations and surgical interventions[6].

Administration of Mannitol in Hepatic Encephalopathy – Oral and Intravenous

Reducing ammonia production in the digestive tract can be achieved by orthograde administration of mannitol solution (2000 ml - 10% per day) via a nasogastric tube until bleeding from digestive hemorrhages subsides[3].

In a study involving 30 patients, mannitol enemas were found to reduce oxidative stress, plasma ammonia levels, and hepatic encephalopathy with less abdominal discomfort[6]. Intestinal administration of mannitol is a safe and well-tolerated therapeutic alternative for improving encephalopathy in chronic liver disease.

Intravenous mannitol administration is recommended as a first-line osmotic agent[7] for treating intracranial hypertension attributed to traumatic brain injury, intracerebral hemorrhage, and hepatic failure. In a study involving 112 patients with 184 episodes of cerebral hypertension, mannitol demonstrated superior effects compared to hypertonic saline[8].

Osmotherapy is one of the fastest methods to reduce water content in brain tissue, with mannitol being the most popular agent used for this purpose. Mannitol is administered intravenously at doses of 1 g/kg. During the use of mannitol, the plasma osmolarity will be monitored to maintain levels within 300-310 mOsm/l.

A controlled study of 44 patients was undertaken to evaluate the use of dexamethasone and intravenous mannitol (1 g/kg) for managing cerebral edema in fulminant hepatic failure. The diagnosis of cerebral edema was based on intracranial pressure recordings or the presence of defined clinical signs. Cerebral edema developed in 34 patients with a similar frequency to those treated with and without dexamethasone (16 of 21 and 18 of 23, respectively). Among the 34 patients, episodes of cerebral edema resolved significantly more frequently in the 17 patients who received mannitol compared to those who did not. Dexamethasone did not affect survival, but patients who developed cerebral edema and received mannitol had significantly better survival rates compared to those who did not (47.1% vs. 5-9%)[9].

Mannitol increases the osmolarity of cerebral capillaries, drawing water from brain tissue into the capillaries, significantly reducing cerebral edema and improving survival. Boluses of 20% mannitol at 1 g/kg body weight are preferred. Plasma osmolarity must be kept below 320 mOsm/l[10].

Parenterally administered mannitol draws water from astrocytes into the intravascular space, potentially stabilizing patients with cerebral edema until liver transplantation[11]. It also improves cerebral oxygenation by increasing cerebral blood flow and enhances survival in patients with hepatic encephalopathy and normal renal function[12].

CONCLUSIONS

Cerebral edema is one of the most frequent causes of death in hepatic failure, and if not controlled through repeated administration of mannitol, death occurs in the majority of cases (90%) within the first 12 hours[12].

Mannitol can be beneficial by lowering plasma ammonia levels when administered enterally and reducing cerebral edema when administered parenterally.

Future studies are needed as there is currently limited data on the benefits of mannitol administration, both enteral and parenteral, in hepatic encephalopathy.

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