5-FU Induced Hyperammonemic Encephalopathy

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BACKGROUND

- Hyperammonaemic encephalopathy (HE) is a serious delayed, adverse side effect induced by 5-fluorouracil usually occurring 1.5-4 days after the start of chemotherapy.[1]
- 5-fluorouracil is an antimetabolite pyrimidine analog used primarily to treat various forms of cancer, particularly in slow growing cancers like ovarian, colorectal, gastric, and breast cancers. The adverse side effects include nausea, vomiting, diarrhea, stomatitis, neutropenia, and thrombocytopenia – due to bone marrow suppression, mucositis, myelosuppression, hand-foot syndrome, rarely cardiac toxicity.[1] One of the rarer side effects that can occur due to 5-FU is (HE).
- Encephalopathy describes a disease effecting the function and/or structure of your brain. There are several different types, some of them are permanent and some of them are reversible/temporary.

INTRODUCTION

- 5-FU induced (HE) is a metabolic condition that manifests as altered mental status with elevated ammonia levels and no hepatic involvement. Whereas hepatic encephalopathy has a completely different etiology, by ruling out liver involvement, we can distinguish the types of encephalopathy from one another. Hyperammonemic and hepatic encephalopathy are easily confused for one another since both of them lead to cognitive abnormalities. [1]
- Aggravating factors of 5-FU induced hyperammonemic encephalopathy include renal dysfunction, dehydration, constipation, body weight loss. 1
- Some other medications that can induce hyperammonemic encephalopathy valproic acid, apatinib, regorafenib, sunitinib, and methamphetamines.
- Signs and symptoms include psychomotor, intellectual, and cognitive abnormalities usually evolving to respiratory alkalosis and then metabolic acidosis.

Mechanisms Resulting in Hyperammonemic Encephalopathy

1.Fluoroacetate build up: 5-FU metabolism produces fluoroacetate which inhibits the Krebs cycle which leads to a decrease in ATP production and inhibits the glutamate dependent and ATP dependent urea cycle. Inhibiting the Krebs cycle could also explain the lactic acidosis usually seen in these patients.

2.Chemotherapy is also considered a catabolic state that may unmask metabolic disorders, which could be screened using a plasma amino-acid chromatography

INTRODUCTION

Pathophysiology of 5-FU Induced Hyperammonemic Encephalopathy

- Due to these mechanisms discussed, ammonia levels increase exponentially. Astrocytes convert ammonia to glutamine, however when there is too much ammonia conversion to glutamine, the excess glutamine compromises the astrocyte structure and function, causing astrocyte swelling.
- It is important to note that the astrocytes are in charge of neurotransmission, removal and maintenance of the blood brain barrier, and blood flow. The astrocyte swelling then causes increased intercranial pressure and encephalopathy.
- Additionally, high concentrations of glutamine and ammonia cause cerebral damage, oxidative stress and failure of neurotransmission systems. Furthermore, the astrocyte swelling and oxidative stress leads to cell apoptosis.6

OBJECTIVES

- To recognize the signs, symptoms, diagnostic markers, mechanisms, and treatment of 5-fluorouracil induced (HE).
- To recognize strategies that can be used to successfully rechallenge patients that have recovered from hyperammonemic encephalopathy

METHODS

- Keywords were entered into Pubmed to find papers, MeSH terms such as 5-fluorouracil and (HE) were used.

RESULTS

- In order to treat the patients (HE) we need to decrease the ammonia levels which can be done by giving:

1)Branched chain amino acids (BCAA): which have shown excellent results when administered, aids with ammonia metabolism.

2)Lactulose: decreases the intestinal production and absorption of ammonia.

- After recovering from (HE) the patient will still need to be on chemotherapy for cancer treatment, patients can be rechallenged with:

1.Capecitabine

2.Lowered dose of 5-FU

RESULTS

3. Tegafur-uracil (1:4) molar ratio: by taking tegafur which is an oral 5-FU prodrug with uracil which is a DPD substrate, the 5-FU is slowly released, reducing the side effects of the fluoroacetate, due to slower degradation of 5-FU.

- Most cases of 5-FU induced encephalopathy spontaneously improve, recurrence is possible when given to the same patient. It is hard to find an alternative some meds that have been used as alts are raltitrexed, irinotecan, and oxaliplatin, however the outcomes were disappointing.
- If the provider attempts to rechallenge the patient with 5-FU there are several things that can be given with the 5-FU infusion which can reduce the risk of hyperammonemic encephalopathy

1.Low-protein diet: By restricting protein intake, it leads to less amino acid build up therefore reducing the risk of amino acid build up. A low-protein diet also limits the nitrogen release that occurs due to protein catabolism.

2.Hydration with 5% glucose: Which is done to provide enough energy/ATP without overloading the deficient krebs cycle.

3.Carbaglutamic acid: Which promotes the first step of the urea cycle in an attempt to detoxify ammonia.

4.Sodium benzoate: A nitrogen scavenger, which reduces the ammonia plasma levels.

5.Anaplerotic substrates: To prevent a cataplerotic state oral alpha ketoglutarate and ornithine are given to provide intermediates for the Krebs and urea cycle. The alpha ketoglutarate is a substrate in the krebs cycle while the ornithine converts excess ammonia into urea. aiding with ATP production and ammonium detoxification

6.Vitamins: Such as vitamin B1 to help with protein metabolism, riboflavin to help with nitrogen metabolism, and biotin to decrease blood ammonia

- Essentially the supplements provide the body with as many materials to keep the Krebs cycle going which is important since the Krebs cycle helps with ammonium detoxification. By giving these additional substances we are trying to prevent the reoccurrence of HE.

RESULTS

Overall 5-FU Induced HE prevention strategy recommendations

- There are currently no recommendations for management except for immediate discontinuation of 5-FU infusions associated with hydration and a low-protein diet
- In this case ammonium chelators (sodium benzoate or sodium phenylacetate) could be used or Urea and krebs cycle intermediates
- More research needs to be done in order to identify potential predictive markers of cataplerosis which is indicative of 5-FU induced HE (ex. Plasma lysine)

CONCLUSIONS

- (HE) is a serious, delayed reaction that occurs after the start of chemotherapy, primarily characterized by alterations in mental status.
- Overall survival time post-HE is 4.3 months, with only a few patients surviving past 1 year.
- Since this is such a rare side effect of 5-FU administration there isn't a lot of data or guidelines on how to treat this condition.
- More research should be conducted in order to identify predictive and diagnostic markers in order to prevent this reaction, patients should also be DPD genotyped in order to see if they are at a higher risk of presenting with this side effect.

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