Drug-induced Hyperammonemia (HA)

Aims

- To provide a short overview of drugs capable to induce HA
- To show some pathophysiological background
- To summarize specific treatment options for drug induced HA

This talk will not

- Cover HA & treatment modalities secondary to hepatic failure (including drug-induced hepatic failure)
Definitions - I

- Plasma ammonia conc. can be measured in arterial or venous blood samples, capillary blood samples not reliable
- Blood should be collected in ammonia-free heparinized or EDTA chilled tubes, placed on ice, rapidly delivered to Lab
- Falsely elevated by hemolysis, exposure to room temperature or delayed delivery to Lab
- Normal values in Adults less than 30 µmol/L (20-80 µg/dL), in Children less than 50 µmol/L; levels below 100 µmol/L in context with clinical course

Definitions - II

Common and infrequent causes of HA:

- Increased ammonia production: infections, increased catabolism, GI-bleeding, burns, trauma, sepsis, TPN, cancer
- Reduced hepatic elimination of ammonia synthesized from bacterial species (e.g. ALF, porto-caval shunts, TIPS)
- Drug-induced HA:
  - drugs affecting urea cycle disorders: e.g. Glucocorticoids, VPA, Topiramate, CBZ, chemotherapeutic agents, sulfadiazine/pyrimethamine
  - Acetaminophen and Salicylate (Reye’s syndrome)
  - Glycine-infusion (during TURP-operations)
Definitions - III

Infrequent causes of HA

- Disturbed mitochondrial ß-fatty-acid-oxygenation

- Urea cycle disorders (UCD) (inborn errors of metabolism)
  - Elevated ammonia (i.e. above 100-150 µmol/L), normal blood glucose and elevated anion gap -> suggests an UCD -> check for plasma amino acids, urine organic- and orotic acid
  - UC enzyme-deficiencies, e.g. determined in liver biopsy
  - Idiopathic HA: normal liver function, normal amino-acid-levels - ruling out enzymatic deficiencies of UC -> acquired insufficiency of glutamine synthase: waste nitrogen circulating as ammonia not being converted to glutamine

Idiopathic HA

- e.g. as a result of CTX-induced reduced glutamine synthase expression and / or activity

Glutamate Glutamine

Martinez-Lapiszina et al., JCSN, 2012
VPA-induced HA

- HA and HAE is a well-known, but serious and potentially fatal complication of VPA-treatment (even under therapeutic serum levels, but uncommon) or **VPA-overdose**

- RF: Polypharmacy (esp. Barbiturates, Phenytoin), malnutrition, infancy

- Several mechanisms have been postulated how VPA may induce HAE:
  - VPA directly stimulates renal glutaminase, thereby increasing synthesis of glutamate and ammonia (25%)
  - VPA / metabolites directly inhibit **CPS I**
  - VPA may cause carnitine depletion, affecting β-oxidation of fatty acids, resulting in decreased acetyl-CoA, necessary for NAG synthesis
  - Valproyl-CoA blocks the enzyme **NAGS** -> **NAG** - an essential allosteric activator of **CPS I** - decreases -> impaired metabolism of ammonia via Carbamoyl-P into the UC

**VPA-induced HA**

![Diagram of VPA-induced HA](image)

- Essential solute carrier protein in exchange of Aspartate and Glutamate SLC25A13-Gene
- Slc25a15 gene: Ornithine-citrulline transport protein
- Adopted from Aires CC et al., *J Hepatol* 2011
HA secondary to chemotherapy

- Functional arginine deficiency secondary to increased catabolism (overwhelming the capacity of the UC) after CTX has been proposed

- CTX-induced impairment of CPS-I gene-expression and function (carboplatin and etoposide)

- Alternatively, tumor replacement of normal (liver) cell lines may decrease expression of the OTC-gene, thereby leading to insufficient OTC enzyme synthesis

- OTC-deficiency leads to decreased synthesis of arginine (and accumulation of NH₄⁺)

- This could lead to inhibition of N-acetyl-glutamate synthase (NAGS), leading to HA

Lazier J et al., Curr Oncol, 2014
Laemmle A et al., Mol Gen Metabol 2015

Topiramate (TPM) + VPA = HA?

- Two proposed mechanisms: a pharmacodynamic and a direct toxic effect

  - Pharmacodynamic: VPA interacts with cytochrome P-450 [CYP2C19], decreasing TPM-metabolism eventually leading to toxic levels of TPM

  - Toxic: TPM inhibits type-II and type-V mitochondrial carbonic anhydrase, thereby blocking the UC by decreased synthesis of bicarbonate, necessary for synthesis of carbamoyl-phosphate via CPS-I

Latour P et al., Hum Psychopharmacol Clin Exp, 2004
Topiramate-VPA-induced HA

Blackford MG et al., *J Pediatr Pharmacol Ther*, 2013

Glycine-infusion during TURP

- Glycine-infusion used during transurethral resection of the prostate may contribute to TURP-syndrome
- Fluid overload, electrolyte dysbalances, and CNS-depression due to HA
- The major pathway of glycine catabolism involves the cleavage of glycine to form CO$_2$, Ammonia and N$^5$N$^{10}$ Methylene-tetra-hydro-folate
- Glycine acts therefore as a donor of one carbon fragment
Acetaminophen-induced HA

• Acetaminophen as the parent drug has been demonstrated to induce decrease activity of both, CPS-I and glutamine synthase, as assayed in liver homogenates in vitro.
• This was accompanied by HA indicating, that CPS-I and/or glutamine synthase were inhibited in vivo to an extent sufficient to compromise ammonia clearance.
• Thus, acetaminophen may additionally contribute to HA, irrespective of NAPQI-induced liver failure

Gupta S et al., Toxicol Appl Pharmacol, 1997

Treatment options for drug-induced HA
General treatment options for HA

- **Stop the offending drug (!)**
- Reduce or temporarily stop protein intake (max. 2 d)
- Infusion of dextrose / insulin to avoid catabolism and establish anabolism
- Correction of acid-base-disorders
- Reduction of bacterial grow (e.g. rifaximine)
- Lactulose p.o. and / or Lactulose-enema:
  - Entrapment of NH$_3$ as ammonium ions by lowering pH, increasing fecal nitrogen excretion and inhibiting glutaminase, thereby inhibiting intestinal wall uptake of glutamine and subsequent metabolism to NH$_3$

- Reduce ammonia-synthesis with **phenylbutyrate** or **sodium-benzoate** (loading dose 5.5 g/m$^2$ each, followed by an equivalent maintenance infusion over 24 hrs; costs 10.- €/day)

Metzeler K et al., *Leukemia Research* 2009
### General treatment options for HA

- **“Quadruple-H-therapy”:**
  - **Hyperventilation:** to minimize hyperemic cerebral edema
  - **Haemodiafiltration (MARS):** rapid reduction of ammonia and reduced production by lowering core temperature (no established cut-off); ECTR suggested at VPA conc. >900 [1D] and recommended at VPA conc. >1,300 mg/L [1D]
  - **Hyponatremia:** increases serum tonicity and reduces cerebral swelling
  - **Hypothermia:** reduces pathologically increased cerebral blood-flow
  - **Carglumic acid** (CA; N-Carbamoyl-L-Glutaminic acid; Carbaglu®, 150 mg/kg), a synthetic analog of the product of NAGS may overcome proximal inhibition of the UC; **Caveat:** CA is not labeled for secondary UC disorders; **costs:** 1,300.- €/day

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### Specific treatment options for VPA-induced HA

- Consider infusion of **L-carnitine** - an essential cofactor in the beta-oxidation of fatty acids in deficient patients: 100 mg/kg as a bolus, followed by 50 mg/kg every 8 hours with a maximum of 3 g - although a matter of debate

- Infusion of **L-Arginine-HCl** (1.2 mmol/kg within 90-120 min, followed by 1.2 mmol/kg/day; **costs** 15.- €/day)

  - **L-Arginine** enters the liver via the portal vein and is metabolized to provide ornithine for citrulline and aspartate synthesis and for the priming of the urea cycle

  - **Side effects** of arginine administration include **metabolic acidosis**, nausea, numbness, headache, thrombocytopenia, and low blood pressure

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Rahimi R et al., *Clin Liver Dis*, 2015
Warrillow SJ et al., *Anaesth Intensive Care* 2014
Ghannoum M et al. (EXTRIP), *Clin Toxicology*, 2015

Nissim I et al., *J Biol Chem*, 2005
Bachmann C et al., *Mol Genet Metab*, 2004
Häberle J et al., *Orphanet J Rare Dis*, 2012
VPA-induced HAE

L-Arginine for VPA-induced HA
Thank you for your kind attention!