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October 2024, Volume 56; Issue 5

HYPERAMMONEMIA IN PAEDIATRIC

INTRODUCTION [1]

Hyperammonemia is accumulation of ammonia in the blood. It is a **TIME CRITICAL medical emergency** with the risk of death and serious neurological damage.

It is most commonly associated with inherited disorders of amino acid and organic acid metabolism. However, it may also be seen in liver failure, sepsis, systemic herpes simplex in neonates and drugs (sodium valproate, carbamazepine, leukaemia treatment with asparagine etc.)

RISKS BASED ON AMMONIA LEVEL

Normal ranges of ammonia in a neonate are less than 100 micromol/L and in a child less than 50 micromol/L. [2]

Ammonia is **neurotoxic** where degree (peak ammonia level) and duration of hyperammonaemia is directly related to poor neurological outcomes. [1,2]

Ammonia remains <250 micromol/L	Good outcomes are seen [1]
Ammonia rises above 350 micromol/L	Significant neurological deficit [1]
Ammonia levels above 1000 micromol/L	Very high risk of death or neurological damage [1]

[favpng.com]

SIGNS & SYMPTOMS [1,2]

Neonatal period:
- Vomiting
- Irritability or somnolence
- Poor feeding
- Failure to thrive
- Developmental delay

Older children (presented more often with neurological symptoms :
- Altered behavior
- Signs of intoxication
- Lethargy
- Encephalopathy

[depositphotos]

CAUSES [3]

1) Acute Liver Failure / Injury
- Drug induced liver injury (such as acetaminophen)
- Inborn errors of metabolism (such as Galactosemia, Reye's Syndrome, Fatty Acid Oxidation Disorders)
- Viral infections (such as Enteroviruses, Herpes simplex virus)
- Autoimmune Disease
- Vascular disease (such as Veno-occlusive disease, Budd-chiari syndrome)

2) Urea Cycle Defects
- ~23% of acute hyperammonemia in critically ill children
- Ornithine transcarbamylase (OTC) Deficiency is the most common inherited defect of the urea cycle

3) Organic Acidurias

4) Fatty Acid Oxidation defects

[pedemmorsels.com]

TREATMENT [4]

HYPERAMMONEMIA DUE TO UREA CYCLE DEFECTS

ANTI-HYPERAMMONEMIC DRUGS COCKTAIL

Indication:
1. Ammonia level > 200 micromol/L
2. Symptomatic (encephalopathic)

Loading dose:
- IV Sodium Benzoate 250 mg/kg
- IV Sodium Phenylbutyrate 250 mg/kg
- IV L-Arginine 250 mg/kg

(mix together in D10% to a total volume of 50mls, infuse over 90 min)

Maintanence dose: Same dilution as above but infuse over 24 hours

Note: Keep drugs balance in fridge for next dose (Use till finish) [8]

HYPERAMMONEMIA DUE TO ORGANIC ACIDURIA

Give oral Carglumic acid, 100 – 250 mg/kg/day in divided doses

DIALYSIS

Indication:
1. Ammonia level > 400 micromol/L
2. Symptomatic (encephalopathic)
3. Inadequate reduction/raising NH3 despite drugs cocktail

Hemodialysis or hemofiltration if available.
If not, peritoneal dialysis is the alternative.
Exchange transfusion is not effective.
(Method of choice depends on local availability, experience of medical staff)

MECHANISM OF ACTION [5,6]

SODIUM PHENYLBUTYRATE: A prodrug that is metabolized to phenylacetate, which combines with glutamine to form phenylacetylglutamine, then rapidly excreted by the kidneys and does not require metabolism via the urea cycle. Phenylbutyrate thus provides an "ammonia sink", an alternative pathway for excretion of excess nitrogen and ammonia.

SODIUM BENZOATE: Like phenylbutyrate, sodium benzoate acts as an ammonia sink, eliminating nitrogen by an alternative pathways independent of the urea cycle

L- ARGININE: Reactivate urea cycle, increases ammonia elimination

CARGLUMIC ACID: A synthetic structural analog of N-acetylglutamate (NAG) that activates carbamoyl phosphate synthetase 1 (CPS-1) in the urea cycle that is responsible for the removal of ammonia.

DRUG STATUS IN HOSPITAL USM [7]

Drug	Status in Hospital USM	Price
Inj Sodium Benzoate 2g/10ml	Non Standard With Buffer	RM142.60/amp
Inj Sodium Phenylbutyrate 2g/10ml		RM159.80/amp
Inj L-Arginine 5g/10ml		RM92.70/amp
*Oral Sodium Benzoate 5g/sachet *Oral Sodium Phenylbutyrate 5g/sachet *Oral L-Arginine 5g/sachet	Non Standard	N/A
Oral Carglumic Acid 200mg	Non Standard	N/A

***NOT AVAILABLE** in Hospital USM. Long term treatment includes oral anti-hyperammonemic drugs cocktail (for urea cycle defects). Continuation of treatment (oral) should be referred and discussed with Genetic Specialist in HKL/ other genetic center.

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