British Inherited Metabolic Disease Group

# MEDICINES USED FOR THE TREATMENT OF HYPERAMMONAEMIA

Several medicines are used in urea cycle and related disorders to create an alternative pathway to urea for the excretion of waste nitrogen. These have proved to be an important advance in the treatment of these disorders.

**Sodium Benzoate** is conjugated to glycine to form hippurate which is then rapidly excreted in the urine. Approximately 1 mol of nitrogen is then lost for each mol of benzoate administered. However free benzoate may be detected in the urine, particularly if sodium benzoate is given intravenously.

The standard dose is 250 mg/kg/d in divided doses. This may be increased to 500 mg/kg/d in an emergency. To calculate the quantities and rates of infusions please click here

**Sodium Phenylbutyrate** is first oxidised to phenylacetate and then conjugated with glutamine to form phenylacetylglutamine. This is also excreted in the urine and theoretically 2 mol of nitrogen are removed for each mol of phenylbutyrate given. However there is uncertainty about the conjugation efficiency as many other compounds have been detected after loading (1). The true efficiency may be nearer 1 mol nitrogen to 1 mol of phenylbutyrate but this is disputed (2).The explanation for this discrepancy may be enzyme induction in patients on long term therapy. Further studies are needed.

The standard dose is 250 mg/kg/d in divided doses. This may be increased to 600 mg/kg/d in an emergency. To calculate the quantities and rates of infusions please click here

**Ammonul**® is a proprietary preparation of sodium benzoate and sodium phenylacetate in the same solution that is used outside the UK. The doses are the same as for sodium benzoate and sodium phenylbutyrate. To calculate the doses, go to the specific Ammonul calculator- please click here.

**L-Arginine** is normally synthesised in the urea cycle but in urea cycle disorders it becomes semi-essential so it has to be given to meet normal needs.

In ornithine transcarbamylase deficiency (OCTD) and carbamyl phosphate synthetase deficiency (CPSD) deficiencies the arginine is that necessary for protein synthesis. The dose is usually 100 – 150 mg/kg/day in divided doses with meals.

In citrullinaemia and argininosuccinic aciduria, the arginine replaces ornithine that is not reformed in the cycle as well as for protein synthesis. In emergencies the dose is usually higher, up to 700 mg/kg/day. However such high doses are probably best avoided in the

long term management. The standard dose for these disorders is 300 - 400 mg/kg/d together with sodium benzoate and sodium phenylbutyrate if necessary. Further studies of the treatment and outcome are needed.

To calculate the quantities and rates of infusions please click here

**L-Citrulline** is used in certain disorders to replace arginine. In severe forms of ornithine transcarbamylase deficiency (OCTD) and carbamyl phosphate synthetase deficiency (CPSD) citrulline may be given instead of arginine. The citrulline is converted to arginine utilising one nitrogen molecule. Citrulline is also used in Lysinuric Protein Intolerance as it enters the cell normally and is then converted to arginine.

**N-carbamylglutamate**

N-acetylglutamate is an essential activator of carbamyl phosphate synthetase and its absence the enzyme activity is low. N-carbamylglutamate is an orally active alternative that is used to treat N-acetylglutamate synthetase deficiency and a small number of patients with carbamyl phosphate synthetase deficiency. It is also used for the treatment of hyperammonaemia in organic acidaemias. A single dose of 250 mg/kg may be given in an emergency

**Practical details**

Arginine, Sodium Benzoate and Sodium Phenylbutyrate should be made up separately in 10% glucose in a 50 ml syringe or 500 ml bag (maximum concentration 2.5g in 50mls or 25 g in 500 ml bag) and given by a syringe pump or by an infusion pump piggy-backed (Y- connector) into the main 10% glucose infusion as close to the entry site as possible.

(Outside the UK Ammonul® is widely available. This is a proprietary mixture of sodium benzoate and sodium phenylacetate which must also be diluted as instructed in the data sheet.)

For more details of solutions to be made up in an emergency and rates of infusions please use the calculator. (Click on this link)

References

1. Kasumov T, Brunengraber LL, Comte B, Puchowicz MA, Jobbins K, Thomas K, David F, Kinman R, Wehrli S, Dahms W, Kerr D, Nissim I, Brunengraber H. New secondary metabolites of phenylbutyrate in humans and rats. Drug Metab Dispos. 2004 Jan;32(1):10-9.

2. Dr Sharron E. Gargosky (Ucyclyd Pharma) oral comment at an international meeting in Barcelona 2007

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