Arginine is used in certain conditions accompanied by hyperammonaemia; for further details see below.

Arginine hydrochloride has also been used as an acidifying agent. In severe metabolic alkalosis intravenous doses have been calculated by the formula:

intravenous dose (in grams) =
desired decrease in plasma-bicarbonate concentration (mEq or mmol/litre)
×
[patient's body-weight (in kg)/9.6]

In forced acid diuresis to hasten drug elimination after overdose a suggested dose has been 10 g intravenously over 30 minutes. However, this has the potential to cause myoglobinuria with acute renal failure, and is rarely used.

Arginine may also be used in the form of the acetylasparaginate, aspartate, citrate, glutamate, oxoglurate, tidiacicate (thiazolidine-2,4-dicarboxylate), and timonacicate (thiazolidine-4-carboxylate). Formulation as an arginine salt is used to improve the solubility of a number of drugs, notably analgesics and antibacterials.

◊ References.

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Hyperammonaemia. Hyperammonaemia is a characteristic feature of inborn errors of the urea cycle, caused by defects in the enzymes carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase (causing hyperargininaemia), or *N*-acetylglutamate synthase (NAGS).[1,2] During the urea cycle, waste ammonia, in the form of the ammonium ion, is normally condensed with bicarbonate and ATP to form carbamoyl phosphate which undergoes several more reactions, including one leading to the synthesis of arginine, and ultimate transformation to urea for excretion. Thus, in defects of this cycle ammonia accumulates and arginine synthesis is deficient.[3] Hyperammonaemia is most severe when the enzyme defect occurs in the early steps of the urea cycle, such as in CPS or OTC deficiency, and is less severe at later stages, as in ASL or arginase deficiency.[2] Hyperammonaemia is often associated with respiratory alkalosis in patients with urea cycle disorders.[3]

The basis of treatment is dietary protein restriction, to decrease the requirement for waste nitrogen synthesis,[4] and the use of drugs to stimulate alternative pathways of waste nitrogen excretion.[5,6] These include arginine, citrulline, sodium benzoate, sodium phenylacetate, and sodium phenylbutyrate. In the initial management of severe hyperammonaemia, haemodialysis is preferred over peritoneal dialysis because it is more effective.[3,7]

Arginine supplements are given except in hyperargininaemia.[5,7] Citrulline may be used in some cases instead;[8] it may be useful for CPS and OTC deficiency (in doses of about 170 mg/kg daily or 3.8 g/m^2 daily),[5,6,9] but it is not recommended for patients with ASS or ASL deficiency, as levels of citrulline are already elevated.[5,10] Some recommend citrulline with arginine in acute hyperammonaemia to aid additional removal of nitrogen.[9] For the treatment of acute hyperammonaemia, some recommend a loading dose of arginine 600 mg/kg over 90 minutes pending definitive diagnosis.[3,10] Alternatively, a loading dose of 200 mg/kg or 4 g/m^2 has been advocated for CPS or OTC deficiency,[6,9,10] and 600 mg/kg or 12 g/m^2 for ASS or ASL deficiency.[6,9,10] The same dose as the loading dose is then given over 24 hours, as a constant maintenance infusion,[6,9,10] until conversion to oral medication is made.[10] For long-term management of ASS or ASL deficiency, doses of arginine ranging from 400 to 700 mg/kg daily have been recommended.[5,6,9,10]

Patients also receive treatment with sodium benzoate and sodium phenylacetate[6,10] or sodium phenylbutyrate.[5,6] ASL deficiency can be managed with protein restriction and arginine alone,[6,11] although some still advocate the use of sodium phenylbutyrate.[5,8] When sodium benzoate is conjugated with glycine and excreted as hippuric acid it provides an alternative pathway of nitrogen excretion, while sodium phenylacetate and sodium phenylbutyrate provide a second and even more effective pathway by conjugation with glutamine.[6,7,10] Some consider intravenous sodium benzoate and sodium phenylacetate the treatment of choice in acute hyperammonaemia; sodium phenylbutyrate is recommended for chronic management.[9] In a 25-year, open-label, uncontrolled study, intravenous therapy with sodium phenylacetate and sodium benzoate clearly improved survival in patients with acute hyperammonaemia, with an overall survival rate of 84%; survival was also related to peak plasma ammonium concentration and age. Haemodialysis was also used to control hyperammonaemia, especially in neonates and older patients who were less responsive to intravenous therapy.[12]

It has been suggested that carnitine supplementation (at 100 mg/kg daily[9] either orally or intravenously) should be added to minimise neurological symptoms and toxicity, but its value is uncertain.[4,13] Low carnitine levels have been reported to be uncommon in patients with urea cycle disorders and, in patients treated with sodium benzoate, benzoyl carnitine may form, negating any potential benefit from carnitine supplementation.[8]

Liver transplantation (p.1815) may achieve long-term correction of urea cycle disorders, even in the very young patient, and gene replacement therapy is under investigation.[14]

Hyperammonaemia and hepatic encephalopathy (p.1697) can also arise from other causes[7,13] for which arginine may not be advocated. Carglumic acid (p.2277) is the treatment of choice for patients with hyperammonaemia arising from NAGS deficiency.

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Hypotensive action. Arginine is the physiological precursor of nitric oxide and this has been suggested as an explanation for the hypotensive effect that has been reported in healthy subjects[1-3] and hypertensive patients[1,4] given infusions of arginine, although effects unrelated to nitric oxide generation cannot be excluded.[4]

Oral arginine has also been reported to significantly decrease mean systolic blood pressure in hypertensive patients,[5] in patients on haemodialysis, and in renal transplant recipients.[6] In patients with essential hypertension, a single dose of arginine by mouth had no effect on blood pressure, although it did improve endothelium-dependent flow-mediated dilatation of the brachial artery compared with placebo.[7] In patients with pulmonary hypertension, short-term use of arginine has reduced pulmonary arterial pressure.[8-10]

In pregnant women with pre-eclampsia (see Hypertension, p.1171), plasma-arginine concentrations were found to be markedly reduced compared with control subjects.[11] Arginine infusions of 20 g, given to women with mild to moderate gestational hypertension,[12] and 30 g given to pre-eclamptic women,[13] significantly reduced systolic and diastolic blood pressure, with no adverse effect on fetal heart rate in the one study.[12] In a study of pre-eclamptic women given arginine 12 g daily for 2 days by mouth, no significant differences in diastolic blood pressure were seen compared with those receiving placebo.[14] However, in another study of pre-eclamptic women given 3 g arginine daily for 3 weeks, systolic, diastolic and mean arterial pressure were significantly reduced compared with those taking placebo.[15]

Because of apparent improvement in endothelial function with arginine, some interest has surrounded its potential role in other cardiovascular diseases, such as coronary artery disease and heart failure.[16] Decrease in plasma-cholesterol concentrations has also been reported in 2 hypercholesterolaemic patients given arginine infusions.[17] However, long-term supplementation was found not to be helpful (and possibly harmful) in patients with peripheral arterial disease,[18] and arginine therapy has been implicated in increased mortality when given to patients after myocardial infarction (see under Adverse Effects and Precautions, above).

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Necrotising enterocolitis. A systematic review[1] considered that although there was evidence suggesting that supplementation of the feed of premature neonates with arginine could prevent the development of necrotising enterocolitis (p.173), it was insufficient to recommend the practice without further study.

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Preparations

BP 2008: Arginine Hydrochloride Intravenous Infusion;
USP 31: Arginine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Inteligen†; Laclorene; ***Austria:*** Sangenor; ***Braz.:*** Reforgan; Targifor; ***Fr.:*** Dynamisan; Energitum†; Eucol; Pargine; Sargenor; Tiadilon; ***Ger.:*** Eubiol†; ***Israel:*** Carginine†; ***Ital.:*** Bioarginina; Dynamisan; Sargenor; Sulfile†; ***Malaysia:*** Arginitric; ***Port.:*** Asparten; Bio-Energol Plus; Pan-Astenico R; Sargenor; Sulfile; ***Spain:*** Potenciator; Sargenor; Sargisthene; Sorbenor; ***Switz.:*** Dynamisan; ***USA:*** R-Gene.

Multi-ingredient: ***Arg.:*** Acrea; Holomagnesio Vital; Inteligen Ginseng†; ***Austria:*** Leberinfusion; Rocmaline; ***Braz.:*** Dinavital C; Ornihepat†; Ornitargin; Targifor C; ***Chile:*** Ureadin 30; ***Cz.:*** Citrarginе†; ***Fr.:*** Arginotri-B; Citrarginine†; Epuram†; Fastenyl; Hepagrume; Hepargitol; Rocmaline; Sargenor a la Vitamine C; ***Ger.:*** Glutarsin E†; Polilevo N†; ***Hung.:*** Glutarsin E; Rocmalat†; ***Indon.:*** Sirec; ***Ital.:*** Calciofix; Glutargin†; Ipoazotal Complex; Ipoazotal†; Isoram; Linfoiodine; Polilevo†; Sargenor Plus; Somatron; Tonoplus†; Vitasprint Complex†; ***Spain:*** Dynamogen; Sanieb†; ***Switz.:*** Activital Forte; Arginotri-B; Vitasprint Complex.

Arrowroot

Amylum Marantae; Araruta; Arruruz; Maranta; Pfeilwurzelmehl; Sagú del monte; Yuquilla silvestre.

Profile

Arrowroot consists of the starch granules of the rhizomes of *Maranta arundinacea* (Marantaceae). It has the general properties of starch (p.1968). It has been used as a suspending agent in the preparation of barium meals and has sometimes been used in place of starch in tablet manufacture.

Diarrhoea. In a pilot study in 11 patients with irritable bowel syndrome given 10 mL arrowroot powder three times daily for 1 month, 4 patients reported an improvement in diarrhoea.[1]

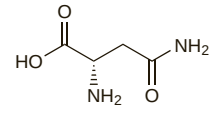
1. Cooke C, *et al.* Arrowroot as a treatment for diarrhoea in irritable bowel syndrome patients: a pilot study. *Arq Gastroenterol* 2000; **37:** 20–4.

Asparagine Monohydrate

L-α-Aminosuccinamic Acid Monohydrate; Asparagiinimonohydraatti; Asparagin monohydrát; Asparagina, monohidrato de; Asparaginas monohidratas; L-Asparagine Monohydrate; Asparagine monohydratée; Asparaginmonohydrat; Asparaginum monohydricum; Asparamide; Aspartamic acid; Aspartic acid beta-amide; N (asparagine); NSC-82391. (2*S*)-2,4-Diamino-4-oxobutanoic acid monohydrate.

$C_4H_8N_2O_3,H_2O$ = 150.1.

CAS — 70-47-3 (anhydrous asparagine); 5794-13-8 (asparagine monohydrate).



(anhydrous asparagine)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF*, which specifies the anhydrous form or the monohydrate.