PYRIDOXINE (Vitamin B_6) **& PYRIDOXAL PHOSPHATE**

Use

Pyridoxine, and its active metabolite pyridoxal phoshate, are used to treat two inborn errors of metabolism that cause convulsions in early infancy. Pyridoxine is also used in the management of homocystinuria.

Biochemistry:

Pyridoxine is widely available in most foodstuffs and nutritional deficiency is extremely rare. Pyridoxine is converted in the body to pyridoxal phosphate, which is a co-factor for a number of enzymes. Pyridoxine dependency is an autosomal recessive condition associated with mutations in the antiquitin (ALDH7A1) gene. This defect leads to the accumulation of piperideine-6-carboxylate, which binds and inactivates pyridoxal phosphate. Pyridoxine dependency should be considered in any baby with severe seizures even if they seem to have a clear cause (e.g. asphyxia). Most cases present soon after birth, and seizures have even been sensed *in utero.* Development may still be delayed even though pyridoxine controls the fits. The diagnosis can be confirmed by measuring CSF plasma or urine alpha aminoadipic semialdehyde (α-ASSA).

Pyridoxine is converted to pyridoxal phosphate by pyridox(am)ine phosphate oxidase, and patients with the rare recessive defect of *this* enzyme present with neonatal seizures that respond to pyridoxal phosphate, but *not* to pyridoxine. It should be noted that pyridoxine and pyridoxal phosphate also display anticonvulsant activity in some patients who do not have either of these conditions for reasons that are not yet understood.

Homocystinuria most commonly results from cystathionine β-synthase deficiency. Pyridoxal phosphate is the co-factor for this enzyme, and many patients improve biochemically and clinically with pharmacological doses of pyridoxine. Cases of homocystinuria detected by neonatal screening programmes, however, tend not to be pyridoxine responsive. Other patients present with developmental delay, or subsequently with dislocated lenses, skeletal abnormalities or thromboembolic disease.

Diagnostic use

Defects of Pyridoxine metabolism: One 100 mg IV dose of pyridoxine stops most fits within minutes. Watch for apnoea. The test is best conducted while the EEG is being monitored (although visible seizure activity may cease some hours or even days before the EEG trace returns to normal), but this test should not be delayed if monitoring proves hard to organise. If the response is negative, or equivocal, and pyridoxine dependency is a likely diagnosis, then oral pyridoxine should be given for two weeks. Finally a trial of pyridoxal phosphate (see below) should be considered in patients who do not respond to pyridoxine.

Fits later in infancy: Some patients with pyridoxine dependency present when more than four weeks old. All infants with infantile spasms or drug-resistant seizures merit a trial of pyridoxine or pyridoxinal phosphate (50 mg/kg of either drug by mouth once a day for a minimum of 2 weeks).

Homocystinuria: Pyridoxine responsiveness should be assessed by measuring plasma methionine and homocysteine under basal conditions, and during a 2–3 weeks trial of pyridoxine, while ensuring a constant protein intake. The dose depends on the patient's age: 150 mg a day in infancy; 750 mg a day in an older child. Give 5 mg folic acid a day to be sure the response is not impaired by folate deficiency.

Treatment

Fits: Infants with fits that respond to pyridoxine should then receive 50–100 mg indefinitely once a day if tests show excess α-ASSA in the urine. The prognosis for siblings may be improved if mothers with a pyridoxine dependent child take 100mg of pyridoxine daily in any subsequent pregnancy.

Homocystinuria: Pyridoxine responsive infants are usually given 50 mg twice a day; older patients are usually given 50–250 mg twice a day and 5 mg of folic acid once a day. If this does not completely correct the abnormality, treatment can be combined with a low methionine diet, betaine (q.v.) and/or vitamin B_{12} (q.v.). These forms of treatment can also be used in patients unresponsive to pyridoxine.

Adverse effects

The first dose of pyridoxine or pyridoxal phosphate in a neonate can cause hypotonia or apnoea requiring support. High doses in adults have caused a sensory neuropathy (and might be neurotoxic in children), so long term management should be overseen by a paediatric neurologist or metabolic physician.

Supply

Pyridoxine: All units should have access to a stock of 2 ml (50 mg/ml) IV ampoules. They cost about £1 each. A sugar-free oral suspension is available, as are 10, 20 and 50 mg tablets (costing 2p each).

Pyridoxal phosphate: 50 mg tablets cost 12p each; a sugar-free suspension is also available.

References

See also the relevant Cochrane reviews ©

Wang H-S, Kuo M-F, Chou M-L, *et al.* Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. *Arch Dis Child* 2005;**90**:512–5. (See also 441–2.)

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