PYRIDOXINE (VITAMIN B6) AND PYRIDOXAL-5-PHOSPHATE FOR TREATMENT OF SEIZURES

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Pyridoxine (vitamin B6) and pyridoxal-5-phosphate (P5P) are co-factors of transamination and decarboxylation reactions in various biochemical pathways involved in neurotransmission including serotonin and dopamine biosynthesis.
- Defects in pyridoxine and pryridoxal-5-phosphate pathways result in neurological phenotypes; specifically neonatal and infantile onset seizures that are responsive to treatment with pyridoxine and /or pyridoxal-5-phosphate.
- Pyridoxine should be tried in all cases of early-onset intractable seizures and status epilepticus with no structural cause; high doses may be necessary in the initial phases to control seizures.
- Pyridoxine over-dosage induces toxic effects.
  - There is the risk of cardiovascular collapse with apnoea when administered by intravenous injection and rarely when administered orally or enterally. Resuscitation facilities must be available and close monitoring of pulse, respiratory rates and blood pressure are recommended.
  - The most common side effect is sensory neuropathy when given in high doses (>500 mg daily) for extended periods
  - Children administered oral doses of pyridoxine for brief periods (days) rarely have side effects
- Refractory neonatal seizures not responsive to pyridoxine may be responsive to pyridoxal-5-phosphate (P5P) due to a rare deficiency of the Pyrido(am)ine 5'-phosphate oxidase enzyme (PNPO)
- Late presentations are described (eg children treated for >28days); a small group of neonates, following initial response to anticonvulsant therapy, become refractory to anticonvulsant but respond to either pyridoxine or P5P; others are late responders – with no or little initial response.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st December 2020	**Review Period**: 3 years
Team Leader:	Staff Specialist	**Area/Dept**: Neurology SCH

Date of Publishing: 19 November 2020 2:17 PM Date of Printing: 19 November 2020

CHANGE SUMMARY

- Triple therapy for PDE – pyridoxine, lysine restricted diet and L arginine supplementation
- Changed dose limit of P5P from 30 mg/kg/day to 15-50 mg/kg/day due to the risk of liver impairment and cirrhosis.
- Recommend blood level of P5P if P5P doses are high or given by IV administration

READ ACKNOWLEDGEMENT

- The following staff are to read and acknowledge they understand the contents of this guideline:
  - Paediatric Neurologists
  - Medical Geneticists and Metabolic Physicians;
  - Paediatric and Neonatal Intensivists;
  - Critical Care nursing staff;
  - Junior Medical Staff;
  - AUM and Educational CNC of C2S (SCH Neurology and Neurosurgery ward) and Commercial Travellers Ward CHW;
  - Nursing staff involved in the care of neonates and children with epilepsy and intractable seizures
  - Pharmacists

TABLE OF CONTENTS

Abbreviations

Antiquitin (ALDH7A1 or Aldehyde dehydrogenase 7 family, member A1) gene

Pyridoxine = vitamin B6

(P5P) Pyridoxal-5-phosphate

(PNPO) Pyrido(am)ine 5'-phosphate oxidase enzyme

(PDE) Pyridoxine-dependent epilepsy

(AASA) Alpha aminoadipic acid semialdehyde

(P6C) L-delta piperideine-6-carboxylate

(GABA) Gamma amino butyric acid

(CSF) Cerebrospinal fluid

(HVA) Homovanillic acid

(HIAA) Hydroxyindoleacetic acid

Introduction

Pyridoxine-Dependent Epilepsy (PDE)

Pyridoxine-dependent epilepsy (PDE) was first described in 1954. It is an autosomal recessive disorder due to mutations in the Antiquitin gene; the exact incidence is still unknown. Estimates vary from 1:20,000 infants with epileptic encephalopathy to 1:600,000 in patients in the UK.

Antiquitin deficiency is the major cause of PDE. The antiquitin gene encodes an enzyme that facilitates cerebral lysine catabolism. To date there have been more than 40 different mutations within the 18 exons of the Antiquitin gene (ALDH7A1 gene). Antiquitin deficiency results in accumulation of chemical substrates arising from lysine degradation proximal to the deficient enzyme activity including alpha aminoadipic acid semialdehyde (AASA) and its cyclic equivalent L-delta piperideine-6-carboxylate (P6C). It is the P6C compound that inactivates pyridoxal-5-phosphate (P5P) which leads to severe cerebral pyridoxal phosphate deficiency and disturbed co-factor function within amino acid and neurotransmitter metabolism including glutamate synthesis, conversion of glutamate into GABA, pipecolic acid degradation and serine formation.

Triple therapy of pyridoxine, diet and arginine is a new approach to pyridoxine-dependent epilepsy [16, 17]. Patients with PDE have benefitted with dietary lysine restricted diet to limit the substrate that leads to neurotoxic metabolite accumulation and co-supplementation with L-arginine to compete for brain lysine influx and liver mitochondrial import [17]. There are case reports that there have been improved neurodevelopmental outcomes for patients with PDE treated with triple therapy [16].

Presentation of PDE

Patients with PDE usually present with seizures soon after birth; in utero convulsions have been reported. Multiple seizure types have been described and there is a high risk of status epilepticus in affected individuals[1]. EEG patterns may vary from normal to high voltage delta activity, focal spike and wave discharges or even burst suppression patterns. Neuro-imaging may show agenesis of the corpus callosum, cerebellar hypoplasia, cortical atrophy, hydrocephalus or intra-parenchymal haemorrhage.

Patients with PDE often demonstrate signs of encephalopathy with marked irritability, sleeplessness, and emesis mimicking signs of drug withdrawal. Seizures are typically refractory to common anticonvulsants but may have a partial response to phenobarbital. Seizures usually recur upon pyridoxine withdrawal.

Diagnosis of PDE

AASA and P6C in urine (and plasma and CSF) serve as diagnostic markers of Antiquitin deficiency. Elevated pipecolic acid is another diagnostic marker but this compound is a relatively heterogeneous and elevations may reflect other conditions such as peroxisomal disease. As AASA and the P6C dimer remain elevated even while pyridoxine is being administered, pyridoxine withdrawal is not necessary for biochemical confirmation of Antiquitin deficiency. AASA is an unstable compound in urine and needs to be frozen immediately. P6C is the most reliable marker in diagnosis of PDE.

Pyridoxal-5-phosphate-Responsive Seizures

Pyridoxal-5-phosphate (P5P)-responsive seizures are caused by autosomal recessive mutations in the Pyrido(am)ine 5'-phosphate oxidase enzyme (PNPO) gene located in chromosome 17q21.32 . This gene encodes the enzyme pyridox(am)ine 5'-phosphate oxidase that converts pyridoxine and pyridoxamine into P5P, the active form of the vitamin B6 cofactor involved in essential amino acid metabolism and production of serotonin and dopamine which are essential in neurotransmission. Pyridoxal-5-phosphate (P5P) is a co-factor for over 100 enzymes involved in amino acid and amine metabolism, three of which are L-aromatic amino acid decarboxylase, the glycine cleavage system and threonine dehydratase. PNPO deficiency can be fatal in the first year and rare survivors have severe neurological handicap and profound brain atrophy. [15]

Classic presentation of PNPO deficiency

PNPO deficiency classically presents in neonatal seizures up to 2 weeks of age. The seizures are generally myoclonic and may evolve into status epilepticus. Patients have a severe epileptic encephalopathy often with an Ohtahara phenotype. The EEG pattern usually shows burst suppressed pattern. Broader organ involvement including anaemia, vomiting, coagulopathy, failure to thrive and renal dysfunction may also occur. MRI changes suggestive of HIE may be noted in some patients such as white matter oedema, possible haemorrhage and laminar necrosis[2]. Microcephaly may be evident in older patients diagnosed after the neonatal period[3].

Diagnosis of PNPO deficiency

Diagnosis of PNPO deficiency is usually initially suggested by a response to P5P administration. If suspected, a trial of P5P should be tried. It is established by low P5P levels in plasma and CSF. Diagnostic blood levels are available locally at Royal Prince Alfred Hospital Chemical pathology laboratory (95154631). Diagnosis is confirmed by molecular analysis of the PNPO gene. A variety of secondary biochemical findings are described including lactic acidosis, elevated glycine and elevated threonine in both plasma and CSF amino acid profiles, as well as low CSF homovanillic acid (HVA), low CSF hydroxyindoleacetic acid (HIAA) or high CSF vanillactate levels and increased CSF L-DOPA and CSF 3-methoxytyrosine; however, these may also be present in other causes of P5P depletion. However, it should be noted that in some patients these results may be normal, Pipecolic acid, 6PC and AASA are typically normal.

Unlike in pyridoxine dependent seizures, diagnostic samples need to be obtained prior to administration of P5P if PNPO deficiency is considered.

Dosing and Presentation

Pyridoxine Dependent Epilepsy

Common practice is to treat PDE initially with a trial of pyridoxine for at least 48 hours or until the urine P6C dimer result is available. If seizures remain refractory, then a trial of P5P and/or folinic acid is recommended. The duration of the P5P trial is currently unclear as there are children with delayed responses to treatment. P5P often makes children vomit. Also an LP can be performed while on pyridoxine.

Optimal effectiveness of pyridoxine therapy occurs when administration is initiated at a time when the patient is actively experiencing seizures.

Preparations of Pyridoxine

- **IV Injection:** Pyridoxine (Vitamin B6) 50mg/2mL and 100mg/2ml preparations are available at the time of writing of this guideline.
- Completion of SAS Category A or B form for submission to the TGA is required for IV Injection formulation.

- **TAB:** pyridoxine 25mg, 100mg scored tablet

Dosage

Initial dose

- For the first suspected trial of pyridoxine in a neonate thought to have pyridoxine-dependent seizures
- Can be administered by IV, IM, ORAL routes

- **Neonate:** initial test dose 50-100 mg/dose (not dosed per kilogram), preferably orally, may be repeated; if responsive this may be followed by oral maintenance dose of 50 mg - 100 mg once daily, adjusted as necessary.
- **Child (1 month to 18 years):** Initial test dose 50 - 100 mg orally daily; followed by an oral dose of 25 mg to 50 mg 1-2 times a day or 100 mg daily, adjusted as necessary; doses up to 30 mg/kg or 500 mg daily have been used.
- Urine P6C dimer should be collected and sent to Victorian Clinical Genetics Service Biochemical Lab.

Maintenance dosing

- Oral therapy preferred for maintenance dosing.
- Even with inconclusive or absent effect, pyridoxine should be continued on 50-100mg daily OR 15-30 mg/kg/day (**max 200 mg/day in neonates and 500 mg/day in adults**) usually given in 2-3 divided doses over 3 consecutive days to detect atypical cases or slow responders. [11]
- The usual daily dose is 100 mg daily.
- When a child is febrile and seizure frequency increases, the maintenance dose has been doubled (i.e. 200 mg daily) for the first 3 days of illness [18].

Pyridoxal-5-phosphate (P5P) Responsive Seizures

Preparations of Pyridoxal-5-phosphate (P5P)

- **Capsule:** 50 mg (also contains Vitamin C 2 mg)
- **IV Injection:** Pyridoxal phosphate 10mg/1mL INJECTION (Pydoxal)
- Completion of SAS Category A or B form for submission to the TGA is required for both Capsule and IV INJECTION formulations of P5P.

Dosage

For suspected Pyridoxal-5-phosphate dependent seizures:

- **ORAL:** Start with a dose of 50 mg/kg/day (Dose ranges of 15-30 mg/kg/day) divided in three to four doses enterally (max of 500 mg daily).[9, 11]
- **IV:** Start with a dose of 0.5 mg/kg/dose (dose ranges up to 40 mg for a 70 kg patient)
- P5P has been used intraoperatively with an IV infusion of 40 mg/hr and it is advised strongly to obtain expert advice from a paediatric neurologist. [14]

The need for IV treatment of P5P deficient children requires expert advice from a paediatric neurologist regarding IV dosing as there is very little information in the medical literature

Doses beyond 30 mg/kg/day need close consideration and assessment of blood levels, given the hepatotoxicity and risk of cirrhosis. Blood levels can be performed by discussion with senior staff at Biochemical genetics at CHW.

Seizure response occurs typically after 2 days of treatment.

There are probably cases who manage on a lower dose of P5P but this should be judged on the basis of EEG and resolution of seizures [9,10,13]. Different mutations probably have different levels of PNPO activity and may tolerate lower doses. The aim should be to manage on the lowest dose to avoid episodes of encephalopathy as there is a risk of cirrhosis. It is unclear whether the encephalopathy in PNPO deficiency is always seizure-related.

The need for IV treatment of P5P deficient children requires expert advice from a paediatric neurologist regarding IV dosing as there is very little information in the medical literature. [13]

The IV dose of P5P needed is substantially lower than the oral dose because a lot of the oral P5P can't be metabolised by the liver and instead is excreted as pyridoxic acid.

Administration

Generally within minutes of a single intravenous dose of 20-100 mg, there are both clinical and EEG evidence of pyridoxine's effectiveness. Intravenous trials of pyridoxine and P5P must take place within a high medical acuity environment or an ICU setting as profound CNS depression with associated changes in the EEG have been noted with some patients after the initial treatment with pyridoxine.

Some clinicians also conduct an initial oral trial of pyridoxine. If a patient does not respond to an initial oral dose of 100 mg, up to 500 mg of pyridoxine can be administered in sequential doses of 100 mg every 5-10 minutes before concluding that the infant's clinical and electrographic seizures are not responsive to pyridoxine. EEG monitoring and seizure response to initial doses of pyridoxine are often not reliable indicators to conclude that a child is not pyridoxine dependent as there are some children who show a delayed response.

An alternative diagnostic approach is suggested for patients experiencing frequent short anticonvulsant-resistant seizures. In these cases, oral pyridoxine (up to 30mg/kg/day) should be prescribed and patients should have resolution within 3-7 days.

P5P needs to be administered immediately and not left sitting in solution as it rapidly degrades to potentially toxic and biologically ineffective breakdown products[5].

P5P be consumed as a whole capsule where possible and that any suspension or solution is taken immediately.

The important issues with IV P5P is that it needs to be given with 0.9% sodium chloride. It needs to be light protected.

Monitoring and Precautions

The same precautions should be undertaken for both pyridoxine and P5P as both are biologically active.

Apnoea and comatose state with depressed amplitudes on EEG following the initial dosage of intravenous or oral/enteral pyridoxine have been observed.

Resuscitation equipment and monitoring of respiratory rate, heart rate and blood pressure is mandatory with the first administration of pyridoxine or P5P.

Seizures usually cease but treatment may be complicated by the onset of hypotonia, respiratory and neurological depression. These symptoms in general subside with a few days and definitive cessation of seizures is the usual outcome, provided therapy is continued.

There has been a case report of a newborn with P5P deficiency who developed worsening encephalopathy and status epilepticus while on prophylactic treatment with oral pyridoxine suggesting high-dose treatment with pyridoxine may result in increased rather than decreased neuro-excitability in these patients [21]. Postnatal prophylactic pyridoxine treatment of foetuses and neonates at risk for PDE should be limited to the shortest possible time, by either prenatal diagnosis or immediate postnatal biochemical and genetic testing. [21]

Toxicity

The minimum acute oral toxic dose for humans is unknown. Two adults who received greater than 2 g/kg IV over 3 days developed severe sensory neuropathy, weakness and autonomic dysfunction. A single intravenous dose of 10 grams has caused neuropathy in an adult. Chronic ingestion of 200 mg to 9600 mg daily for months to years has resulted in neuropathy in adults.

Pyridoxine doses of up to 500 mg daily were reported to be safe in children [11].

Higher doses of pyridoxine (>500 mg daily) may cause a reversible sensory (and rarely also motor) neuropathy and nerve conduction studies may be helpful to monitor this potential side-effects. It is unclear what the risk of peripheral neuropathy is in treated PNPO deficiency.

Large doses of pyridoxal phosphate and pyridoxine have been reported to cause loss of appetite, restlessness, vomiting, diarrhoea and drowsiness. It is important to monitor liver function tests (LFTs) in patients taking P5P as there is a risk of cirrhosis.

Until further evidence becomes available, it is suggested that the dose of PLP is carefully titrated against symptoms with close monitoring of liver function especially when doses greater than 50 mg/kg/day are used. [5,19]

References

1. Plecko B Handbook of Clinical Neurology 113 (3rd series) Pediatric Neurology Part III chapter 185 Pyridoxine and pyridoxal phosphate-dependent seizures p1811- 1817
2. Mills PB et al 2014 Epilepsy due to PNPO mutations : genotype, environment and treatment affect presentation and outcome Brain :
3. Mills PB et al 2005 Neonatal epileptic encephalopathy caused by mutations in the PNPO gene encoding pyridox(am)ine 5'-phosphate oxidase Human Molecular Genetics 14(8): 1077-1086.
4. McLachlan RS and Brown WF 1995 Pyridoxine dependent epilepsy with iatrogenic sensory neuropathy Can J Neurol. Sci. 22: 50-51.
5. Sudarsanam A et al 2014 Cirrhosis Associated with Pyridoxal 5' Phosphate Treatment of Pyridoxamine 5'-Phosphate Oxidase Deficiency JIMD reports
6. Joint Formulary Committee. *British National Formulary* for children (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com.acs.hcn.com.au> [Accessed on 25/02/2020]
7. van Karnebeek, 2015 Current Treatment and Management of Pyridoxine-Dependent Epilepsy Current Treatment Options in Neurology 17:2 p1-12.
8. Pascual JM 2008 Epilepsy in Inherited Metabolic Disorders. The Neurologist 14 (65) S2-S14.
9. Gospe SM 2010 Neonatal Vitamin-responsive Epileptic Encephalopathies Chang Gung Med J. 33: 1-12.
10. Baxter P 2001 Pyridoxine-dependent and pyridoxine responsive seizures Dev. Med. Child. Neurol. 43: 416-420.
11. Stockler S et al., 2011 Pyridoxine dependent epilepsy and antiquitin deficiency Clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. Molecular Genetics and Metabolism 104: 48-60.
12. Wang HS et al., 2005 Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy Arch Dis Child 90:512-515.
13. Mastrangelo M 2018 Actual Insights into Treatable Inborn errors of Metabolism causing epilepsy J Pediatric NeuroSci 13(1):13-23
14. Personal communication, Dr Richard Webster.
15. Surtees,R and Wolf N 2007 Treatable neonatal epilepsy Arch Dis Child 92: 695-661.
16. Coughlin CR et al., 2015 Triple therapy with pyridoxine, arginine supplementation and dietary lysine restriction in pyridoxine-dependent epilepsy: Neurodevelopmental outcome. Molecular Genetics and Metabolism 116 (1):35-43.
17. Van Karnebeek CDM et al., 2014 Lysine-Restricted Diet as Adjunct therapy for Pyridoxine Dependent Epilepsy : the PDE Consortium Consensus Recommendations JIMD Reports 15: pp 47-57.
18. Rahman, S Footitt EJ, Varadkar, S and Clayton PT 2013 Inborn errors of metabolism causing epilepsy DMCN 55(1) p23-36
19. Mohamed-Ahmed, AHA, Wilson MP, Albuera M, Chen T, Mills PB, Footitt EJ, Clayton PT, and Tuleu C 2017 Quality and stability of extemporaneous pyridoxal phosphate preparations used in the treatment of paediatric epilepsy https://doi.org/10.1111/jphp.12701
20. McLachlan RS & Brown WF 1995 Pyridoxine dependent epilepsy with iatrogenic sensory neuronopathy Canadian Journal of Neurological Sciences 22(1); pp50-51 https://doi.org/10.1017/S0317167100040506
21. Hartmann H Fingerhut M, Jakobs C, Plecko B 2011 Status epilepticus in a neonate treated with pyridoxine because of a familial recurrence risk for antiquitin deficiency: pyridoxine toxicity? DMCN 53(12) pp 1150-1153 https://doi.org/10.1111/j.1469-8749.2011.04033.x