Pyridoxine
Newborn use only

2021

Alert	There is a risk of apnea and cardiovascular collapse with IV pyridoxine and rarely with oral pyridoxine. Resuscitation facilities must be available and close monitoring of pulse, respiratory rates and blood pressure are recommended with starting dose. IV Pyridoxine is a Special access Scheme (SAS) product.
Indication	Treatment of suspected or confirmed pyridoxine dependent epilepsy.
Action	Water soluble B vitamin. Pyridoxal phosphate (PLP) is the biologically active coenzyme form of pyridoxine. PLP is required for glutamic acid decarboxylase (GAD) enzyme activity. GAD is required for the formation of gamma-aminobutyric acid (GABA). GABA is an inhibitory neurotransmitter in cerebral cortex.
Drug type	B vitamin
Trade name	Pyridox oral tablet Streuli (SAS) injection
Presentation	ORAL: 25mg tablet IV: 100mg/2mL (SAS)
Dose	**Initial dose (for therapeutic or diagnostic purpose)** IV route recommended. 100 mg/dose (NOT PER KILOGRAM) (1) Infants <2000 g: 30 mg/kg/dose IV and if no response after 10 minutes, further dose can be given to a total dose of 100 mg (NOT PER KILOGRAM)* (ANMF expert group consensus)(1-3,9) *May need further doses if no/partial response– To discuss with neurologist on call. **Maintenance dose** ORAL or IV: 15-30 mg/kg/day once a day to a maximum of 200 mg/day in neonates (ANMF expert group consensus) (1-3,9)
Dose adjustment	If a definite clinical response is established with IV or IM, oral pyridoxine should be initiated and continued as per the advice of neurologist.
Maximum dose	200 mg/day in neonates
Total cumulative dose	
Route	Oral, IV, IM
Preparation	**ORAL** Tablet is freely soluble in water. Crush the whole 25 mg tablet and disperse in 5 mL of water (=5 mg/mL). **IV** Use undiluted **IM** Use undiluted
Administration	ORAL: May be given at any time with regard to feeds IV Injection: Give slowly over 5 minutes IM Injection (oral is preferred)
Monitoring	Continuous cardiorespiratory monitoring EEG monitoring with initial dose A pyridoxine level of < 20 nanomoles/L is indicative of deficiency.
Contraindications	Hypersensitivity to pyridoxine.
Precautions	Initial dose is to be given in facilities with resuscitation facilities. Use with caution in neonates with existing hypotension, marked sedation and respiratory disorders.
Drug interactions	Pyridoxine may decrease the level/effect of: phenobarbital and phenytoin.
Adverse reactions	Cardiovascular collapse and apneoa Central nervous system: Drowsiness, headache, neuropathy, paraesthesia, seizure (following very large IV doses). The major long term concern is peripheral neuropathy and children on long term treatment with pyridoxine should be periodically assessed by having their ankle jerks tested while on treatment. Endocrine & metabolic: Acidosis, folate deficiency. Gastrointestinal: Nausea Hepatic: Increased serum AST Skin reactions: can enhance existing acne vulgaris or cause an acne-like dermatitis. Hypersensitivity reaction.
Compatibility	Fluids: No information. Y site (5): Amikacin, calcium chloride, calcium gluconate, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, clindamycin phosphate, dexamethasone sodium phosphate, digoxin, dobutamine, dopamine, doxycycline,

	enalaprilat, epinephrine hydrochloride, Epoetin alfa, erythromycin lactobionate, fentanyl citrate, fluconazole, gentamicin sulfate, heparin sodium, insulin regular, lidocaine hydrochloride, magnesium sulfate, metoclopramide, midazolam hydrochloride, morphine sulfate, naloxone hydrochloride, nitroglycerine, nitroprusside sodium, norepinephrine bitartrate, papaverine hydrochloride, penicillin G potassium, penicillin G sodium, piperacillin sodium, potassium chloride, propranolol hydrochloride, protamine sulfate, ranitidine hydrochloride, sodium bicarbonate, streptokinase, succinylcholine chloride, theophylline, ticarcillin disodium, tobramycin sulfate, tolazoline hydrochloride, urokinase, vancomycin hydrochloride, vasopressin, verapamil hydrochloride (4).
Incompatibility	Fluids: No information. Y site (5,6): Amphotericin B conventional colloidal, Ampicillin, Azathioprine, cefazolin, diazepam, diazoxide, folic acid, furosemide, ganciclovir, hydralazine, hydrocortisone sodium succinate, imipenem-cilastatin, indometacin, methylprednisolone sodium succinate, oxacillin sodium, phenobarbital, phenytoin sodium, sulfamethoxazole-trimethoprim.(4,5)
Stability	Protect from light. Do not refrigerate or freeze.
Storage	Store at or below 25°C
Excipients	Nil
Special comments	
Evidence	**Background** Pyridoxine-dependent epilepsy (PDE-ALDH7A1) is an autosomal recessive condition due to a deficiency of α-aminoadipic semialdehyde dehydrogenase, which is a key enzyme in lysine oxidation. PDE-ALDH7A1 is a developmental and epileptic encephalopathy. Pharmacologic dose of pyridoxine remains central to the treatment of seizures. However, not all patients respond immediately to a trial of pyridoxine. Patients may present with concomitant findings such as hypoglycemia and lactic acidosis, and may also present with seizures after the neonatal period. Despite adequate seizure control, most patients with PDE-ALDH7A1 were reported to have developmental delay and intellectual disability.(1) **Efficacy** Neither the best route nor the best dose is clearly known in neonates.(9) 2020 International PDE Consortium consensus guidelines: All newborns with PDE-ALDH7A1 are treated with pyridoxine supplementation. **Newborns** should be treated with 100 mg/day of pyridoxine supplementation. **Infants** should be treated with 30 mg/kg/day of pyridoxine supplementation with a maximum dose of 300 mg/day. These guidelines do not provide a dose recommendation for preterm infants, although consortium group notes that (1) intravenous pyridoxine is not without risk as apnea and comatose state have been reported after the initial Iv dose, (2) lower doses of pyridoxine have been reported, and (3) the recommended dose of pyridoxine for long term management was 15-30 mg/kg/day in infants and up to 200 mg/day in neonates.(1) Baxter et al. reported that the use of a higher starting dose of pyridoxine (above 18 mg/kg bodyweight per day) is associated with a fall in IQ, whereas a starting dose below 15 mg/kg bodyweight per day is associated with a higher IQ score. It has been suggested to individualise the dose of pyridoxine based on IQ testing.(2,3) Augmentation of the dose of pyridoxine has also been recommended during episodes of fever or gastrointestinal illness.(6) **Safety** There is a risk of cardiovascular collapse with apnoea when administered by intravenous injection and rarely when administered orally or enterally.(9) Acute depression of neurological and respiratory function, bradycardia, hypothermia, hypotonia and apnoea, as well as depression of cerebral electrical activity, have been reported after oral or parenteral test doses of pyridoxine in infants.(6) This is probably due to a rapid increase in cerebral GABA levels, together with a decrease in the levels of glutamic acid, which is an excitatory neurotransmitter. Slow IV infusion over 1 hour has been suggested to reduce the risk of acute deterioration.(6) Long term use has been reported to be associated with reversible sensory neuropathy in adults.(6,7) **Maximum safe dose:** Case reports from older children published varying doses to achieve clinical, EEG and/or biochemical improvement. Baxter et al. in a population based cross sectional survey, found an improvement in the quality of behaviour and IQ following an increase of the dose of pyridoxine between 150 and 500 mg/day (2.5–23.9 mg/kg bodyweight per day).(2) Baumeister et al found the CSF level of glutamate in a 32-month-old child with PDS to be 200-fold the normal level when the child was off pyridoxine. A dose of 5 mg/kg bodyweight per day of pyridoxine caused normalization of the EEG in this child and remission of the seizures, but the concentration of glutamate in the CSF was still 10-fold the

	normal concentration. An increase of the dose of pyridoxine to 10 mg/kg bodyweight per day not only normalized the glutamate levels in the CSF in this case, but was also associated with a normal developmental outcome.(8) Baxter et al. in an open longitudinal study of 5 children over 4 years of age, aimed to determine the optimum dose of pyridoxine in PDE by performing annual IQ assessments.(3) Higher starting dose of pyridoxine (above 18 mg/kg bodyweight per day) was associated with a fall in IQ, and doses of pyridoxine up to 15 mg/kg per day were safe. **Pharmacokinetics** Oral pyridoxine is reabsorbed with a time peak concentration in 1.25 hours. Half-life of pyridoxine is 15-20 days.(4)
Practice points	
References	1. Coughlin CR, Tseng LA, Abdenur JE, Ashmore C, Boemer F, Bok LA, et al. Consensus guidelines for the diagnosis and management of pyridoxine-dependent epilepsy due to α-aminoadipic semialdehyde dehydrogenase deficiency. Journal of inherited metabolic disease. 2021;44(1):178-92. 2. Baxter P, Griffiths P, Kelly T, Gardner-Medwin D. Pyridoxine-dependent seizures: demographic, clinical, MRI and psychometric features, and effect of dose on intelligence quotient. Developmental Medicine & Child Neurology. 1996;38(11):998-1006. 3. Baxter P, Kelly T, Gardner-Medwin D. Pyridoxine-dependent seizures: Doses up to 15 mg/kg/day can improve IQ. Dev Med Child Neurol Suppl. 1999;82(5). 4. Pyridoxine. Micromedex online. Accessed on 21 January 2021. 5. Pyridoxine. Australian Injectable Drugs Handbook, 8th edition. Accessed on 21 January 2021. 6. Gupta V, Mishra D, Mathur I, Singh K. Pyridoxine-dependent seizures: A case report and a critical review of the literature. Journal of paediatrics and child health. 2001;37(6):592-6. 7. Gospe Jr SM. Current perspectives on pyridoxine-dependent seizures. The Journal of pediatrics. 1998;132(6):919-23. 8. Baumeister FA, Shin YS, Egger J, Gsell W. Glutamate in pyridoxine-dependent epilepsy: neurotoxic glutamate concentration in the cerebrospinal fluid and its normalization by pyridoxine. Pediatrics. 1994;94(3):318-21. 9. Baxter P, editor. Vitamin responsive conditions in paediatric neurology. Cambridge University Press; 2001 Jan 16.

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Authors Contribution

Original author/s	Srinivas Bolisetty, Bhavesh Mehta
Evidence Review	Srinivas Bolisetty
Expert review	Richard Webster, Bindu Parayil Sankaran, Shekeeb Mohammad, Michael Cardamone, Karel Allegaert
Nursing Review	Eszter Jozsa, Kirsty Minter
Pharmacy Review	Sarah Woodland, Jessica Mehegan, Mona Mostaghim, Pathma Joseph, Mohammad Irfan Azeem
ANMF Group contributors	Nilkant Phad, John Sinn, Cindy Chen, Michelle Jenkins, Simarjit Kaur, Helen Huynh, Priya Govindaswamy
Final editing and review	Thao Tran, Srinivas Bolisetty
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty