Phosphorus
Newborn use only

2021

Alert	Most often given in conjunction with calcium for the prevention and treatment of metabolic bone disease in preterm infants. 1 mmol phosphorus/phosphate (P) = 31 mg elemental phosphorus. 1 mmol elemental calcium (Ca) = 40 mg elemental calcium. Separate oral doses from calcium supplements by at least 1 hour. When using IV preparation, always check plasma sodium and potassium concentrations to assist in choosing the right phosphate preparation (e.g. sodium or potassium phosphate preparation).
Indication	Treatment of Metabolic Bone Disease. Treatment of hypophosphataemia. Supplementation to meet the recommended daily intakes.
Action	Phosphorus is a major intracellular mineral and is important in bone mineralisation and energy production.
Drug Type	Mineral
Trade Name	Phosphate-Phebra® oral effervescent tablets Each tablet contains: 16.1 mmol phosphate (equivalent to 500 mg elemental phosphorus); 20.4 mmol sodium; 3.1 mmol potassium Sodium dihydrogen phosphate Phebra IV (preferred IV preparation) Each 10 mL vial (sodium dihydrogen phosphate 1.56 g) contains: 10 mmol phosphate; 10 mmol sodium; 20 mmol hydrogen Potassium dihydrogen phosphate concentrated injection DBL IV Potassium dihydrogen phosphate concentrated injection Phebra IV Each 10 mL ampoule (potassium dihydrogen phosphate 1.361 g) contains: 10 mmol phosphate; 10 mmol potassium; 20 mmol hydrogen
Presentation	Oral: 500 mg effervescent tablets; IV preparation (e.g. sodium or potassium dihydrogen phosphate) can be given orally. IV: Sodium dihydrogen phosphate 10 mL vial; Potassium dihydrogen phosphate concentrated injection 10 mL ampoule.
Dose	**Treatment of metabolic bone disease (MBD)** PO: 1 to 3 mmol/kg/day in 2-4 divided doses as an addition to intake from milk and other sources to a maximum intake of 4.5 mmol/kg/day. Use either Sodium dihydrogen phosphate Phebra IV preparation or Phosphate-Sandoz tablets. **General principles of treatment of MBD:** A. Commence at low dose (e.g. 1 mmol/kg/day) and titrate the dose up as tolerated. B. Given in conjunction with calcium supplementation (but not together - example: **Calcium** 8 AM, 2 PM, 8 PM and **Phosphorus** 6 AM, 12 MD, 6 PM) C. Aim to reach the upper end of the recommended intake: Ca 5 mmol/kg/day and P 4.5 mmol/kg/day.[8] D. Dose can be adjusted with a goal of slight excess supply aiming for urinary calcium ≥1.2mmol/L and phosphate ≥0.4 mmol/L. **Treatment of acute hypophosphataemia** IV: 0.2 mmol/kg/dose [range 0.15–0.33 mmol/kg/dose] over 6 hours. Repeat as necessary. Aim to maintain normophosphataemia of 1.8–2.6 mmol/L (5.6–8.1 mg/dl). **Daily enteral Supplementation to meet the recommended daily intakes (RDI)** 2–4.5 mmol/kg/day (62–140 mg/kg/day of phosphorous)[7,8] 1. Calculate intake from parenteral and enteral sources 2. Supplement the difference via IV or oral route.

Dose adjustment	
Maximum dose	
Total cumulative dose	
Route	PO IV
Preparation	**Oral** Option 1 (preferred option for infants going home or when a long storage time is required in the NICU): Disperse 500 mg (16.1 mmol) Phosphate-Sandoz in 16 mL of water for injection to make a solution with a concentration of 1 mmol/mL. Option 2 (can be used where preparation with low osmolality is preferred e.g. infants with history of feed intolerance): IV sodium dihydrogen phosphate decanted into a bottle and given orally undiluted (expiry time: 7 days). **IV infusion for treatment of acute hypophosphataemia:** IV infusion (sodium dihydrogen phosphate): Draw up 1 mL (1 mmol phosphate) and add 19 mL sodium chloride 0.9% or glucose 5% to make a final volume of 20 mL with a concentration of 0.05 mmol/mL. Draw up 4 mL/kg (0.2 mmol/kg). IV infusion (potassium dihydrogen phosphate): Draw up 1 mL (1 mmol phosphate) and add 24 mL sodium chloride 0.9% or glucose 5% to make a final volume of 25 mL with a concentration of 0.04 mmol/mL. Draw up 5 mL/kg (0.2 mmol/kg).
Administration	**Oral** Can be administered with feeds (refer to evidence summary section). Separate calcium supplements by at least 2 hours. **IV** **As part of parenteral nutrition fluid** – refer to individual parenteral nutrition formulations. **IV infusion for treatment of acute hypophosphataemia:** IV sodium dihydrogen phosphate or IV potassium dihydrogen phosphate: Infuse over at least 6 hours. For severe hypophosphataemia infuse over 8–12 hours. Maximum infusion rate of 0.2 mmol/kg/h.
Monitoring	Phosphate, calcium, magnesium, alkaline phosphatase concentrations are required at least fortnightly or more often if required. Once these concentrations normalise, serum analysis may be performed once monthly for 6 months or at the discretion of the clinician.[10] Urinary calcium and phosphate and Tubular Reabsorption Phosphate (TRP)%, parathormone, and vitamin D concentrations may be useful under certain circumstances .
Contraindications	Hyperphosphataemia, dehydration, severe renal insufficiency, shock.
Precautions	Hypernatraemia (avoid sodium dihydrogen phosphate). Hyperkalaemia (avoid potassium dihydrogen phosphate)
Drug Interactions	Calcium and magnesium antacids (e.g. acetate, carbonate, citrate, hydroxide etc.) reduce phosphate absorption — separate doses by at least 2 hours. Additive effects with other drugs that may prolong QT interval. Potassium dihydrogen phosphate preparation may increase the risk of hyperkalaemia when used in conjunction with potassium sparing diuretics (e.g. spironolactone).
Adverse Reactions	Diarrhoea (oral use only), hypocalcaemia, nephrotoxicity, prolonged QT interval, hypotension, hypomagnesaemia. Hyperphosphataemia – carpopedal spasm, seizures. [2]
Compatibility	<u>Potassium dihydrogen phosphate</u> Fluids: Glucose 5%, glucose 10%, glucose in sodium chloride solutions, sodium chloride 0.45%, sodium chloride 0.9%, sodium chloride 3%. Y-site: No information. <u>Sodium dihydrogen phosphate</u>

	Fluids: Glucose 5%, sodium chloride 0.9%. Y-site: No information
Incompatibility	Potassium dihydrogen phosphate Fluids: No information Drugs: Aciclovir, amiodarone, calcium salts, ketamine, lorazepam, magnesium salts, rocuronium. Solutions that contain other cations such as calcium, magnesium, iron and aluminium may also precipitate. Sodium dihydrogen phosphate Fluids : No information Drugs: Aciclovir, amiodarone, calcium salts, calcium, aluminium or magnesium, iron and magnesium containing solutions.
Stability	Preparation from oral effervescent tablets: It is to be used immediately after preparation and discard unused portion. Oral preparation from IV sodium dihydrogen phosphate: 7 days
Storage	Store below 25°C.
Excipients	Phosphate-Phebra® oral effervescent tablets: Sodium bicarbonate, potassium bicarbonate, macrogol 4000, citric acid, sucrose, orange 52570 TP0551 and saccharin sodium.
Special Comments	
Evidence	**Recommended daily intakes (RDI)** Phosphorus absorption is typically 80% to 90% of dietary intake.[3] **Parenteral intake:** Previously, the recommended doses of **parenteral** Ca and P in preterm infants varied from 1.3–3 mmol Ca/kg/day and 1.0–2.3 mmol P/kg/day, with a Ca:P ratio in the range of 1.3–1.7.[1,4-6] ESPGHAN 2018 updated guidelines on parenteral nutrition recommends the following Ca and Phosphate:[12]

	Parenteral Ca mmol (mg)/kg/day	**Parenteral** Ph mmol (mg)/kg/day
Preterm during the first days of life	0.8-2.0 (32-80)	1.0-2.0 (31-62)
Growing preterm	1.6-3.5 (100-140)	1.6-3.5 (77-108)
Term neonate	0.8-1.5 (30-60)	0.7-1.3 (20-40)

Enteral intake: ESPGHAN 2010 Guidelines for enteral nutrition recommend 2–3 mmol/kg/day of a highly absorbable phosphate source in a ratio with calcium (Ca:P) of 1.5–2.0.[7] American Academy of Pediatrics Committee on Nutrition 2013 Guidelines recommend Ca 150-200 mg/kg/day (3.8-5 mmol/kg/day) and P 75-140 mg/kg/day (2.4-4.5 mmol/kg/day) and 200-400 IU/day of vitamin D for enteral nutrition in preterm neonates.[8]

The exact serum phosphorus concentration at which to commence supplementation of phosphate is not known and recommendations vary from 1.3 mmol/L[8] to 1.8 mmol/L.[9]

Metabolic bone disease
Goal: Aim for the upper end of the recommended range to prevent fractures and clinical symptoms of osteopenia: Ca and P of around 4-4.5 mmol/kg/day. Adjust the mineral intake with a goal of achieving a slight excess of urinary mineral excretion: Urinary calcium ≥1.2mmol/L and phosphate ≥0.4 mmol/L.[14]

Step 1: Calculate the mineral intake from enteral feed:
Example: 150 ml/kg/day of mature preterm EBM contains: Ca 1 mmol/kg/day and P 0.6 mmol/kg/day. 150 ml/kg/day preterm EBM+24kcal HMF contains: Ca 4.5 mmol/kg/day and P 2.7 mmol/kg/day.

Preterm milk	Ca, mmol (mg)/100 mL	P, mmol (mg)/100 mL
1st week	0.7 (26)	0.4 (11)
2nd week	0.6 (25)	0.5 (15)

Week 3/4	0.6 (25)	0.5 (14)
Week 10/12	0.7 (29)	0.4 (12)
Term milk		
1st week	0.7 (26)	0.4 (12)
2nd week	0.7 (28)	0.6 (17)
Week 3/4	0.7 (27)	0.5 (16)
Week 10/12	0.7 (26)	0.5 (16)

Elemental Ca, 1 mmol = 40 mg. Elemental Phosphorus, 1 mmol = 31 mg. Adapted from Gidrewicz and Fenton BMC Pediatrics 2014, 14:216.[15]

Step 2: Calculate the gap in Ca and P intake/requirement: This will be the dose required.

Step 3: Prescribe 50% of the required dose of Ca and P in 2-3 divided doses alternatively but not together. (example: Ca 8 AM, 2 PM, 8 PM and P 6 AM, 12 MD, 6 PM).

Step 4: Once 50% dose is tolerated for 1 week, increase to 100% required dose.
ORAL preparation during NICU stay: Sodium dihydrogen phosphate Phebra IV is the preferred preparation for oral administration due to its low osmolality.
ORAL preparation at discharge or stable neonates: Phosphate-Sandoz tablets can be used.

American Academy of Pediatrics Committee on nutrition 2013 Guidelines on management for Enterally Fed Preterm Infants With Radiologic Evidence of Rickets: 1. Maximize nutrient intake. 2. If no further increases in these can be made, add elemental calcium and phosphorus as tolerated. Usually beginning at 20 mg/kg per day of elemental calcium and 10–20 mg/kg per day elemental phosphorus and increasing, as tolerated, usually to a maximum of 70–80 mg/kg per day of elemental calcium and 40–50 mg/kg per day elemental phosphorus. May consider targeting 25-OH-D concentration of >20 ng/mL (50 nmol/L).[8] However, breast milk content of phosphorus is variable and harder to estimate the intakes accurately. A more pragmatic approach suggested by our consensus group: start with P 0.5-1.0 mmol/kg/day in divided doses and increase as tolerated to a maximum of P 3 mmol/kg/day.

Efficacy and safety
An ideal oral form of phosphate for use in preterm infants does not exist. Administering the intravenous preparations orally can be considered, because they are lower in osmolarity than are commercially available phosphorus-containing liquids. For example, potassium dihydrogen phosphate provides 31 mg of elemental phosphorus per millimole. A dose of 10 to 20 mg/kg per day of elemental phosphorus is reasonable and will likely resolve hypophosphataemia in most preterm infants.[8]

Oral phosphorus and feeds
It is recommended to separate oral doses from calcium and antacids containing agents such as aluminium hydroxide, calcium or magnesium salts, as these may reduce the bioavailability of phosphate. Oral phosphate preparation has high osmolality and administration with feeds may have theoretical benefit of reducing the osmolality (consensus opinion).

Practice points

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