Alert

Multiple forms of calcium exist with varying amounts of elemental calcium expressed in varying units. Therefore careful attention is required in prescription and administration of calcium to avoid over- or under-dosing. Conversion factor for elemental Ca: 1 mg = 0.025 mmol = 0.05 mEq.

Do not give calcium solutions and sodium bicarbonate simultaneously by the same route to avoid precipitation.

Do not mix with any medication that contains phosphates, carbonates, sulfates or tartrates. Separate doses of the following by at least 2 hours: phosphate, iron, thyroxine and phenytoin.

CalSource Effervescent tablets were discontinued in 2019.

Indication

Oral calcium supplement to prevent / treat calcium deficiency.

Asymptomatic hypocalcaemia.

Action

Calcium is essential for the functional integrity of the nervous, muscular, skeletal and cardiac systems and for clotting function.

Drug type

Mineral.

Trade name

Caltrate 600mg, Cal-600 tablets: Calcium carbonate 1500mg (contains elemental calcium 600mg)

AUSPMAN 100mg/mL calcium carbonate suspension [1mmol/mL(40 mg/mL) of elemental calcium]

If required:

Calcium Gluconate Injection (Phebra) (calcium 0.22 mmol/mL).

Calcium Chloride Injection (Phebra) 10% (calcium 0.68 mmol/mL).

CalSource Effervescent tablets were discontinued in 2019, but SAS product (Calcium (SAS) (Sandoz Fortissimum) 1 g Effervescent tablet) is available.

Presentation

Caltrate 600, Cal-600: Calcium carbonate 1500mg (contains elemental calcium 600mg)

AUSPMAN 40mg/mL (1mmol elemental calcium/mL) calcium (carbonate) suspension

If required:

Calcium gluconate 10% 10 mL vial contains 0.22 mmol/mL of elemental calcium.

Calcium chloride 10% 10 mL vial contains 0.68 mmol/mL of elemental calcium.

Dose

Dose can vary.

Estimate the calcium intake from all sources before prescribing oral calcium.

Recommended total daily intake of elemental calcium from all sources: 120–200 mg/kg/day (3–5 mmol/kg/day).

Usual starting oral calcium dose: 20 mg/kg/day (0.5 mmol/kg/day). Can increase up to 80 mg/kg/day (2.0 mmol/kg/day). Divide the daily dose into 2-4 doses mixed with feeds (Do not mix with Phosphate – See Drug Interactions).

Dose – Special scenarios

Not applicable.

Maximum dose

Oral – 5.5 mmol/kg

Total cumulative dose

Oral

Route

Preparation

AUSPMAN suspension – no further dilution necessary

Caltrate, Cal-600: Calcium carbonate 1500mg (contains elemental calcium 600mg)

Crush and dissolve one tablet in 30 mL of water. This will give a solution containing 0.5 mmol/mL (20mg/mL). The relevant dose should be calculated and withdrawn by oral syringe immediately on complete dispersion of tablet (so as not to let dispersed liquid settle). Any remaining liquid should be discarded. Please refer to Appendix A.

Calcium Effervescent tablet: Dissolve one calcium 1000 mg effervescent tablet in 10 mL of sterile water to make a 2.5 mmol/mL solution.

Administration

Administer with feeds.

If required, calcium IV vials may be given orally (must be diluted at least 1:4 with sterile water).

Monitoring

Monitor calcium, phosphate and magnesium. Measurement of ionised calcium preferred over total calcium.

Correct hypomagnesaemia if present.

Contraindications

Caution in patients with renal or cardiac impairment

Precautions

Do not mix with any medication that contains phosphates, carbonates, sulfates or tartrates.

Drug interactions

Do not mix with any medication that contains phosphates, carbonates, sulfates or tartrates. Separate doses of the following by at least 2 hours: Phosphate, iron, thyroxine and phenytoin.
Digoxin (serious risk of arrhythmia and cardiovascular collapse), thiazide diuretics (increased risk of hypercalcaemia), ketoconazole (decreased ketoconazole effect).

**Adverse reactions**
Nephrolithiasis with long term use.
Gastric irritation, diarrhoea and NEC have occurred during oral therapy with hyperosmolar preparations (must dilute with water).

**Compatibility**
Do not mix with any medication that contains phosphates, carbonates, sulfates or tartrates.

**Stability**
Oral solution: Discard remaining after use.
Calcium gluconate is a supersaturated solution and may precipitate in the vial at room temperature. Inspect the vial before use.

**Storage**
Caltrate 600mg tablets: Store below 25°C.
Cal-600 tablets: Store below 25°C.
AUSPMAN suspension: Store below 25°C.
Calcium Gluconate Injection (Phebra): Store below 30°C. Do not refrigerate.
Calcium Chloride Injection (Phebra): Store below 25°C.

**Excipients**
Caltrate tablets: Excipients not listed.
Cal-600 tablets: Excipients not listed.
AUSPMAN suspension: Hydroxybenzoate.
Calcium Gluconate Injection (Phebra) (calcium 0.22 mmol/mL): Excipients not listed.
Calcium Chloride Injection (Phebra) 10%: Sodium hydroxide and/or hydrochloric acid may be used for pH adjustment.

**Special comments**
Hypocalcaemia defined as a serum total calcium concentration below 1.875 mol/L [7.5 mg/dL] or ionized calcium less than 1.2 mmol/L.[1]

Blood gas machines measure ionised calcium directly and are more accurate than the main pathology laboratory which calculates the ionised calcium from a complex formula. Corrected calcium is calculated (when albumin < 40 or > 45) by the formula:

\[
\text{Measured Ca (mmol/L)} + (40 – \text{albumin (g/L)} \times 0.025)
\]

**Calcium salt equivalents of elemental calcium**

<table>
<thead>
<tr>
<th>Salt</th>
<th>Elemental Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium chloride 10% 1 mL</td>
<td>1.36 mEq</td>
</tr>
<tr>
<td>Calcium gluconate 10% 1 mL</td>
<td>0.46 mEq</td>
</tr>
<tr>
<td><strong>Salt 1g</strong></td>
<td></td>
</tr>
<tr>
<td>Calcium Acetate</td>
<td>12.6 mEq</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>19.9 mEq</td>
</tr>
<tr>
<td>Calcium Citrate</td>
<td>10.5 mEq</td>
</tr>
<tr>
<td>Calcium Chloride</td>
<td>13.6 mEq</td>
</tr>
<tr>
<td>Calcium Glubionate</td>
<td>3.29 mEq</td>
</tr>
<tr>
<td>Calcium Gluceptate</td>
<td>4.08 mEq</td>
</tr>
<tr>
<td>Calcium Gluconate</td>
<td>4.65 mEq</td>
</tr>
</tbody>
</table>

**Evidence**
**Efficacy**
Recommended mineral intake:
One mmol of calcium (Ca) equates to 40 mg calcium and 1 mmol of phosphorus equates to 31 mg phosphorus (P).[2] A 1:1 Ca:P molar ratio is equal to 1.3: 1 weight (mg) ratio. Transplacental Ca and P delivery to the fetus occurs actively against a concentration gradient and is greatest after the 24th gestational week. It is estimated that 80% of mineral accretion occurs in the 3rd trimester of pregnancy.[3] The average accretion rates during the last 3 months of pregnancy are 3 mmol/kg/day of Ca and 1.9 mmol/kg/day of P.[4]

For prevention and treatment of metabolic bone disease in premature infants, the goal is not only to maintain normal serum levels but also mimic in utero bone accretion rates for calcium and phosphorus.[5] The recommended calcium intake is 150 to 220 mg/kg per day [3.7 to 5.5 mg/dL].
mmol/kg/day] and phosphorus 75 to 140 mg/kg per day [2.4 to 4.5 mmol/kg/day] to provide a calcium-to-phosphorous ratio less than 2:1. Although no optimal calcium-to-phosphorous ratio is identified, a 1.5 to 1.7:1 ratio may be optimal for preterm infants.[6] There is a concern that an intake of calcium 5 mmol/kg/day may be associated with nephrocalcinosis.[7]

Infants on full feeds with multicomponent fortified human milk (or preterm formula) reach an optimal level of mineral intake with approximately 180-220 mg/kg/day calcium and 100-130 mg/kg/day phosphorus.[5]

Oral mineral supplementation: A single RCT in 40 premature human milk fed infants compared oral calcium gluconate 10% 5ml/kg/day (45mg/kg/day of elemental divided 8 hourly), potassium phosphate 17% 1 ml/kg/day (24 mg/kg/day divided 12-hourly) and vitamin D 400 U daily versus a control group that received only vitamin D 400 U daily. Although serum alkaline phosphatase concentration was reduced in the group receiving supplementation at six weeks postnatal age, the difference is unlikely to be of clinical significance.[8, 9] A second control study compared calcium intake varied from 2.5 versus 3.75 versus 5 mmol/kg/day combined with phosphate 2.5 mmol/kg/day. Low calcium intake was associated with raised alkaline phosphatase. High calcium intake was associated with nephrocalcinosis.[7] Conclusion: A calcium intake of 3.75 mmol/kg/day in combination with phosphate 2.5 mmol/kg/day is sufficient for adequate bone mineralization with a low level of side effects.[7] Further trials of mineral supplementation are not recommended as supplementation with multicomponent human milk fortifiers is now usual.[8]

Optimising mineral supplementation: In infants with mineral deficiency serum calcium is protected by increased parathyroid hormone so is not useful for optimising intake. Reaching target mineral intakes through optimised use of multicomponent human milk fortifiers for enterally fed infants lowers the probability of developing metabolic bone disease in preterm infants.[10] For infants with hypophosphatemia, phosphorus supplementation can be adjusted to reach a target serum phosphorus of >5.5 mg/dl [1.8 mmol/L].[5] An alternative method to optimise mineral intake is to supplement calcium and phosphate with the goal of achieving a slight surplus of supply (SSS).[11] In infants not on diuretics or methylxanthines, this is achieved by regular adjustments to 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.[11-13]

Supplementation with calcium and phosphorus when further increase cannot be made in diet alone: Calcium starting dose 20 mg/kg/day; maximum dose 70 to 100 mg/kg/day. Phosphate starting dose 10-20 mg/kg/day; maximum dose 40 to 50 mg/kg/day.[5]

Hypocalcaemia:

Hypocalcaemia may be defined as a serum total calcium concentration <1.875 mmol/L (7.5 mg/dL) or ionized calcium < 1.2 mmol/L.[1] Calcium concentrations decrease transiently after birth.[14-16] Early neonatal hypocalcaemia occurs within the first 3 days of life and is common in premature infants with 26% to 50% having levels < 1.75 mmol/L (7 mg/dL).[14-16] Most infants will be asymptomatic, with hypocalcaemia detected only on routine chemistries. They may present with symptoms of neuromuscular irritability including tremulousness, tetany, exaggerated startle response, seizures and laryngospasm, and nonspecific symptoms such as apnea.[1, 15] Treatment of hypocalcaemia: In normocalcaemic infants, a randomised trial of calcium chloride 10% (2.5 mg/kg) vs calcium gluconate 10% (7.5 mg/kg) reported an equal effect on calcium concentrations.[17] However, in 49 critically ill, hypocalcaemic infants (age 1 day to 17 years), calcium chloride 0.136 mEq/kg per dose resulted in a greater increase in ionised calcium and blood pressure than calcium gluconate 0.136 mEq/kg per dose. The group receiving calcium chloride had an increase in MAP of nearly 6 mm Hg (p <0.05). No change in blood pressure was seen in the group receiving calcium gluconate.[18] In 104 newborns with late symptomatic hypocalcaemia after artificial feeding with a full-cream evaporated milk were randomly allocated to calcium gluconate 10% 10 ml orally vs phenobarbitone 75 mg 6-hourly orally for 48 hours vs magnesium sulphate 50% 0.2 mL/kg intramuscularly on two occasions 12 hourly. The plasma calcium levels rose in all groups, but infants treated with magnesium sulphate had higher plasma calcium concentrations after 48 hours’ treatment and fewer convulsions during and after the treatment period.[19] Recommendation: Treatment of newborns with acute or symptomatic
hypocalcaemia is accomplished best by the intravenous infusion of calcium salts - 10% calcium gluconate (9.3 mg/mL of elemental calcium) is used most commonly. In asymptomatic newborns, treatment is indicated when the total serum calcium concentration < 1.5 mmol/L (6 mg/dL) in the preterm infant and less than <1.75 mmol/L (7 mg/dL) in the term infant. Calcium supplementation can be given either by the intravenous or oral route, depending on the clinical status of the infant. [1] [Expert opinion].

Safety:
Excessive mineral intake (calcium 5 mmol/kg/day) may contribute to nephrocalcinosis.[7] Calcium gluconate solution in glass containers contains almost 200 times more aluminium than calcium gluconate in plastic containers, due to the solution leaching aluminium from the glass. The Paediatric Medicines Expert Advisory Group recommended that these products should no longer be used for repeated or prolonged treatment of children or those with impaired renal function. [20]

Calcium can slow the heart rate and precipitate arrhythmias. Do not give calcium solutions and sodium bicarbonate simultaneously by the same route to avoid precipitation.[21]

Practice points

References


APPENDIX A
ORAL Calcium preparation

Calcium is widely available as Caltrate® OR Cal-600®. Both contain 600mg elemental calcium. The tablet can be dissolved in freshly boiled but cooled water. Ensure you check the expiry date on the bottle.

1. Using a tablet crusher, finely crush one tablet.

2. In a 30 mL measuring cup, mix the crushed tablet with 30 mL of freshly boiled but cooled water. This will result in a solution containing 20mg elemental calcium per 1 mL. Note that the solution will be cloudy and the tablet may not fully dissolve.

3. Immediately draw up the required dose in an oral syringe and administer to the baby with feeds (do not give at the same time as phosphate, separate by at least 2 hours). The dose will be prescribed by the doctor, depending on the baby’s need. A guide of the different doses (mg) and amount (mL) of solution to give is in the tablet below.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Amount of solution (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg (0.25 mmol)</td>
<td>0.5</td>
</tr>
<tr>
<td>15 mg (0.38 mmol)</td>
<td>0.75</td>
</tr>
<tr>
<td>20 mg (0.5 mmol)</td>
<td>1</td>
</tr>
<tr>
<td>25 mg (0.63 mmol)</td>
<td>1.25</td>
</tr>
<tr>
<td>30 mg (0.75 mmol)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

4. Discard the remainder of the solution. Always use a new tablet for each dose.