Alert

Two of the intravenous preparations of ibuprofen (Neoprofen and Pedea) are not currently registered with the Therapeutic Goods Administration (TGA). They are available for use via the Special Access Scheme (SAS). A category A SAS form will need to be completed for each course prescribed. The third available preparation, Caldolor, is registered for fever reduction, acute mild-mod or mod-severe postop pain (+ reduced morphine dose) in adults.

Indication

Closure of patent ductus arteriosus.

Action

Prostaglandin inhibitor. Prostaglandins are important in maintaining ductal patency in utero.

Drug Type

Non-steroidal anti-inflammatory drug (NSAID).

Trade Name

Intravenous: Caldolor (ibuprofen arginine), Neoprofen (ibuprofen lysine), Pedea (ibuprofen sodium). Oral: Advil, Bugesic, Chemist's Own, Dimetapp, iProfen, Nurofen

Presentation

IV:
Caldolor (ibuprofen arginine) 800 mg/8 mL
Neoprofen (ibuprofen lysine) 20 mg/2 mL
Pedea (ibuprofen sodium) 10 mg/2 mL

Oral: 100 mg/5 mL

Dosage/Interval

<table>
<thead>
<tr>
<th>Post-natal Age</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 72 hours</td>
<td>10 mg/kg/dose</td>
<td>5 mg/kg/dose</td>
<td>5 mg/kg/dose</td>
</tr>
<tr>
<td>≥ 72 hours (Higher dose)</td>
<td>20 mg/kg/dose</td>
<td>10 mg/kg/dose</td>
<td>10 mg/kg/dose</td>
</tr>
<tr>
<td>≥ 72 hours (lower dose)</td>
<td>10 mg/kg/dose</td>
<td>5 mg/kg/dose</td>
<td>5 mg/kg/dose</td>
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</tbody>
</table>

Consider a second course 4 days later if duct does not close within 48 hours of the last dose or if it re-opens.

Maximum daily dose

20 mg/kg

Total cumulative dose

20–40 mg/kg

Route

IV, oral

Preparation/Dilution

Caldolor (ibuprofen arginine)
Draw up 0.5 mL (50 mg of ibuprofen) and add 19.5 mL of sodium chloride 0.9% or glucose 5% to make a final volume of 20 mL with a concentration of 2.5 mg/mL

Neoprofen (ibuprofen lysine)
Draw up 1 mL (10 mg of ibuprofen) and add 3 mL of sodium chloride 0.9% or glucose 5% to make a final volume of 4 mL with a concentration of 2.5 mg/mL

Pedea (ibuprofen sodium)
Can be administered undiluted.
If dilution is required draw up 2 mL (10 mg of ibuprofen) and add 2 mL of sodium chloride 0.9% or glucose 5% to make a final volume of 4 mL with a concentration of 2.5 mg/mL

Administration

IV infusion:
Caldolor (ibuprofen arginine) – over 30 minutes
Neoprofen (ibuprofen lysine) – over 15 minutes
Pedea (ibuprofen sodium) – over 15 minutes.

Do not use chlorhexidine to disinfect the neck of the ampoule.

Oral – give via intra-gastric tube, preferably with milk feed to minimise risk of gastrointestinal irritation. If baby is not on enteral feeds or breast milk is not available, give dose via intra-gastric tube and flush with 0.5 mL water for injection.
**Monitoring**

Monitor urine output, cardiovascular status, serum biochemistry, renal function and for signs of bleeding.

**Contraindications**

Serious infection, active bleeding, thrombocytopenia or coagulopathy, necrotising enterocolitis or intestinal perforation, significant renal dysfunction, ductal dependent congenital heart disease, pulmonary hypertension and significant jaundice as may displace bilirubin from albumin.

**Precautions**

IV – nil

Oral- nil

**Drug Interactions**

Aminoglycosides: Dose may need to be modified as ibuprofen affects renal function.

Fluconazole: Metabolism of ibuprofen may be inhibited, increasing its concentration.

Systemic corticosteroids: Intestinal perforation has been described in infants treated with early dexamethasone and indomethacin. Although not described with ibuprofen, caution is advised.

**Adverse Reactions**

Prophylactic ibuprofen is associated with renal impairment and gastrointestinal haemorrhage. (LOE I). Ibuprofen for treatment of PDA is associated with renal impairment (LOE I). There are case reports of pulmonary hypertension responsive to nitric oxide in infants treated with ibuprofen (LOE IV).

**Compatibility**

Fluids- Caldolor (ibuprofen arginine), Neoprofen (ibuprofen lysine) and Pedea (ibuprofen sodium):

Sodium chloride 0.9%, glucose 5%

Y site:

Neoprofen (ibuprofen lysine): Ceftazidime, frusemide, heparin sodium, potassium chloride.

Pedea (ibuprofen sodium) and Caldolor (ibuprofen arginine): Not tested.

**Incompatibility**

Caldolor (ibuprofen arginine), Neoprofen (ibuprofen lysine) and Pedea (ibuprofen sodium) - regard all other IV solutions and drugs as incompatible.

**Stability**

Caldolor (ibuprofen arginine): Diluted solutions are stable for up to 24 hours at room temperature (20–25° C) and room lighting.

Neoprofen (ibuprofen lysine) and Pedea (ibuprofen sodium): Discard unused portion once opened.

**Storage**

IV – store unopened vials at room temperature (20–25°C).

Oral liquid – store below 25°C.

**Special Comments**

Nil

**Evidence summary**

Effectiveness: Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight infants: Ibuprofen is as effective as indomethacin in closing a PDA and currently appears to be the drug of choice. Ibuprofen reduces the risk of necrotising enterocolitis and transient renal insufficiency compared to indomethacin^4 (LOE I GOR B).

Route: Oro-gastric administration of ibuprofen appears as effective as intravenous administration^4 (LOE 1 GOR C).

Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants: Prophylactic treatment exposes many infants to a drug that has renal and gastrointestinal side effects without conferring important short-term benefits and is not recommended^5 (LOE I GOR C).

Side effects: Prophylactic ibuprofen is associated with renal impairment and gastrointestinal haemorrhage (LOE I). There are case reports of pulmonary hypertension^5 (LOE IV). Ibuprofen may displace bilirubin from albumin at high concentrations in vitro (200 micromol/L)^6. This does not appear to occur in vivo at the concentrations associated with recommended doses (up to 100 micromol/L)^7.

Dose: Two RCTs compared higher-dose (20, 10, 10 mg/kg/day) versus lower dose (10, 5, 5 mg/kg/day) ibuprofen for patent ductus arteriosus in extremely preterm infants with an increase in ductal closure rate reported. There was no difference in side effects. Peak concentrations were 109.8 (S.D 27.2) micromol/L^8. A pharmacokinetic study has shown drug elimination increases...
with postnatal age and recommended ibuprofen course: 10, 5, 5 mg/kg for neonates younger than 70 hours, 14, 7, 7 mg/kg between 70–108 hours and 18, 9, 9 mg/kg between 108–180 hours\textsuperscript{10}.

Recommendation: Consider higher dose regimen (20, 10, 10 mg/kg) after postnatal day 4.

Contraindicated in infants with significant jaundice (LOE II; GOR C).

References