Propranolol
For Infantile Haemangioma
Newborn use only

2019

Alert	For infants with comorbidities that are likely to lead to hypoglycaemia (e.g. hyperinsulinism/preterm/low weight) and for cervico-facial segmental haemangioma – propranolol dose schedule needs to be cautious. Ensure that child is fed regularly to reduce the risk of hypoglycaemia. If feeding is reduced, propranolol needs to be stopped until the child is feeding normally.
Indication	1. Infantile haemangioma (IH) causing/likely to cause compromise or complications. 2. Cervico-facial segmental haemangioma (suspected PHACES syndrome)
Action	The exact mechanism of action is unclear. Suggested actions include pericyte-mediated vasoconstriction, inhibition of vasculogenesis, catecholamine-induced angiogenesis and downregulation of the renin–angiotensin–aldosterone axis.
Drug Type	Beta-adrenergic blocker
Trade Name	Deralin, Inderal tablets Propranolol suspension compounded by pharmacy department.
Presentation	Propranolol (Auspman) 2 mg/mL Propranolol suspension (formulas for multiple concentrations exist) compounded by Pharmacy Department.
Dosage / Interval	**All IH except segmental haemangioma** including facial segmental haemangioma: **Term birth/normal weight/No comorbidities:** Refer to monitoring section prior to the commencement. Starting dose: 1 mg/kg daily in 2–3 divided doses. Maintenance dose: 2 mg/kg daily in 2–3 divided doses. Minimum time interval between dose increases: 24 h **Preterm/low birthweight/comorbidities:** Refer to monitoring section prior to the commencement. Starting dose: 0.5 mg/kg daily in 2–3 divided doses. Maintenance dose: 2 mg/kg daily in 2–3 divided doses. Minimum time interval between dose increases: 24 h **Facial segmental haemangioma** (suspected PHACES syndrome) Refer to monitoring section prior to the commencement. Starting dose: 0.5 mg/kg daily in **3** divided doses. Refer to evidence summary section for further management. **Treatment duration** In many cases, treatment can be stopped at 1 year of age and the majority of patients with IH do not need treatment beyond 17 months of age. It is safe to stop propranolol abruptly (rather than weaning patients off treatment gradually) during or at the end of therapy.
Maximum daily dose	3 mg/kg/day in unresponsive cases.
Route	Oral
Preparation/Dilution	Propranolol (Auspman) 2 mg/mL
Administration	If using suspension compounded by Pharmacy, shake well before measuring dose. To reduce the risk of hypoglycaemia, administer orally during or immediately after a feed.
Monitoring	Prior to commencement of therapy • Cardiovascular and respiratory examination by a competent practitioner is required before starting propranolol (auscultation, peripheral pulses, abdominal examination for potential liver enlargement) • Pre-treatment ECHO needed in selected cases (e.g. segmental haemangioma)

	• Pre-treatment ECG needed in selected cases (e.g. cardiac arrhythmias, segmental haemangioma) • Unless otherwise indicated, routine pre-treatment FBC, renal, liver and thyroid profiles are not required before starting propranolol. • Baseline glucose is only required in selected cases (e.g. infants with hypoglycaemia, IV propranolol) • Paediatric cardiology assessment in selected cases. • Patients younger than 4 weeks of age, who are preterm, with faltering growth, feeding difficulties and/or significant comorbidities, such as hyperinsulinism, previous episodes of hypoglycaemia, respiratory, cardiac, metabolic or neurological disorders, require admission for 2–4 h on initiation and for dose increments >0.5 mg/kg daily: HR and BP measurements should be done immediately before the first dose and then every 30 min for 2–4 h after the first dose. • Blood glucose needs to be checked only in patients at risk of hypoglycaemia. <u>After first dose</u> • Post-first dose monitoring not routinely needed. • Where observation needed (HR and BP), there should be 30 min between observations. • Total length of observation 2–4 hours. • Glucose to be checked only in patients at risk of hypoglycaemia (preterm, low weight, intercurrent illness, faltering growth, neonates, history of hypoglycaemia). Suggested regimen: Blood glucose 8 hourly pre-dose for 48 hours upon commencement. • Bradycardia: Newborns (<1 month old) <70 beats per minute; infants (1–12 months old) <80 beats per minute. <u>During treatment</u> • Routine follow-up for a patient on a stable treatment dose, without complications, should be at intervals of 2–3 months. • BP and HR do not need to be monitored between appointments if the infant is well. <u>Stopping propranolol</u> A. Temporary cessation required if: 1. Significantly reduced oral intake of feeds (due to risk of hypoglycaemia) 2. Wheezing requiring treatment.
Contraindications	Relative Frequent wheezing Blood pressure outside normal range for age – treatment in conjunction with neonatologist/paediatrician/dermatologist HR outside normal range for age or cardiac arrhythmias – treat in conjunction with neonatologist/paediatrician/dermatologist Absolute Hypoglycaemic episodes, recent or ongoing Heart block, second and third degree Hypersensitivity to propranolol
Precautions	Infants with comorbidities that are likely to lead to hypoglycaemia – intercurrent illness, preterm, low birthweight, infants at risk of hypoglycaemia. Segmental haemangioma including PHACES syndrome (posterior fossa malformations–haemangioma–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe) – may increase the haemodynamic risks associated with an otherwise asymptomatic cerebral arteriopathy. Hyperthyroidism — beta-blockers may mask clinical signs, e.g. tachycardia. Phaeochromocytomas — beta-blockers may aggravate hypertension; an alpha-blocker should be given first.

	Beta-blockers may reduce the response to usual doses of adrenaline (epinephrine) for anaphylaxis. Myasthenia symptoms – may worsen. Beta-blockers may worsen first-degree AV block. Beta-blockers may impair peripheral circulation and exacerbate symptoms of peripheral arterial disease (PAD). Beta-blockers may mask important signs of acute hypoglycaemia (e.g. tachycardia, tremor). They may also increase the incidence and severity of hypoglycaemia but data are conflicting. Can precipitate bronchospasm.
Drug Interactions	β-Blockers and cholinomimetics (e.g. neostigmine) cause bradycardia, AV block and hypotension via their synergistic negative chronotropic effect. Propranolol and non-dihydropyridine calcium channel blockers (Verapamil and diltiazem) cause bradycardia, asystole, sinus arrest due to their additive effect on the heart. Propranolol and digoxin cause bradycardia and AV block via their additive effect. Propranolol may prolong the hypoglycaemic effects of insulin and mask the signs of hypoglycaemia. Prostaglandin synthetase inhibiting drugs (e.g. ibuprofen and indomethacin) may decrease the hypotensive effects of β-blockers β-Blockers and dronedarone cause bradycardia as both drugs slow heart rate and dronedarone can inhibit CYP2D6 altering metabolism of some β-blockers. β-Blockers and antipsychotic phenothiazines cause hypotension as they have an additive effect. β-Blockers and propafenone cause profound hypotension and cardiac arrest as they have a similar effect on the heart, propafenone can inhibit metabolism of some β-blockers through inhibition of CYP2D6. Some β-blockers and some SSRIs cause bradycardia, AV blocks and hypotension as fluoxetine and paroxetine are inhibitors of CYP2D6 and thus slow metabolism of some β-blockers. Increase blood levels/toxicity: Inhibitors of CYP2D6 including amiodarone, cimetidine (but not ranitidine), delavudin, fluoxetine, paroxetine, quinidine and ritonavir; and inhibitors of CYP1A2 including imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan and rizatriptan. Decrease blood levels/decrease efficacy: Inducers of hepatic drug metabolism including rifampin, ethanol, phenytoin, and phenobarbital.
Adverse Reactions	May cause transient worsening of heart failure symptoms (e.g. in too fast up-titration). The manifestations of β-blocker overdose include bradycardia, atrioventricular (AV) blockade, hypotension, left ventricular failure and cardiogenic shock. Common (>1%) adverse reactions include bradycardia, hypotension, orthostatic hypotension, transient worsening of heart failure (when treatment starts), nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, exacerbation of Raynaud's phenomenon, fatigue, dizziness, abnormal vision, alteration of glucose and lipid metabolism.
Compatibility	
Incompatibility	
Stability	Auspman propranolol unopened bottle: 2-year shelf life.
Storage	Do not freeze. Protect from light. Auspman preparation: Store below 30°C. Compounded suspension from Pharmacy Department: Refrigerate or store according to instructions on bottle.
Special Comments	Initiation of treatment is recommended after stabilisation of heart failure symptoms. Avoid too fast up titration.

Evidence summary	**Infantile haemangiomas:** A systematic review of interventions for infantile haemangiomas reported that compared with placebo, oral propranolol 3 mg/kg/day improves clinician-assessed clearance (RR 16.61, 95% CI 4.22 to 65.34; 1 study; 156 children; moderate-quality evidence) and results in a clinician-assessed reduction in mean haemangioma volume of 45.9% (95% CI 11.60 to 80.20; 1 study; 40 children; moderate-quality evidence). There was no evidence of a difference in terms of short- or long-term serious adverse events (RR 1.05, 95% CI 0.33 to 3.39; 3 studies; 509 children; low-quality evidence) including bronchospasm, hypoglycaemia or serious cardiovascular adverse events. Comparing topical timolol maleate (0.5% eye drops applied twice daily) versus oral propranolol (via a tablet taken once daily, at a 1.0 mg/kg dose), there was no difference in haemangioma size measured by the proportion of patients with a clinician-assessed reduction of 50% or greater (RR 1.13, 95% CI 0.64 to 1.97; 1 study; 26 participants; low-quality evidence). Although there were more short- or long-term general adverse effects (such as severe diarrhoea, lethargy, and loss of appetite) in the oral propranolol group, there was no evidence of a difference between groups (RR 7.00, 95% CI 0.40 to 123.35; 1 study; 26 participants; very low-quality evidence).[1] ***Conclusion:*** In the management of infantile haemangiomas, oral propranolol and topical timolol maleate are more beneficial than placebo in terms of clearance or other measures of resolution, or both, without an increase in harms. It is uncertain if there is a difference in safety. Oral propranolol is currently the standard treatment for this condition. [LOE I GOR B] **Airway haemangiomas:** Reviews of case series in the literature report that propranolol may be an effective and safe treatment strategy for infantile haemangiomas obstructing the airway.[2,3] [LOE IV GOR C] **2018 British Society for Paediatric Dermatology (BSPD) guidelines:**[4] **Infantile haemangioma:** Majority of IH do not require treatment because spontaneous involution can be expected. Indications for treatment can be divided into three main categories: ulceration, risk of disfigurement and functional impairment. Periocular IH warrants early treatment with propranolol if causing or likely to cause visual impairment. IH of the lip may have an adverse impact on feeding, particularly if ulcerated. Nasal IH blocking the nostril may impact on feeding, as well as breathing. Airway IH can develop in infants who do not have cutaneous lesions. However, the risk of airway IH is higher with segmental IH located in a mandibular, cervico-facial or 'beard' distribution. Treatment with propranolol can be initiated on an outpatient basis without monitoring of HR or BP for infants older than 4 weeks, with no significant comorbidities, born at term, with normal birthweight, established feeds and appropriate weight gain. The starting dose of propranolol is 1 mg/kg/daily in three divided doses. The dose can be increased after 24 h to 2 mg/kg daily in three divided doses. For preterm patients and those with comorbidities, such as hyperinsulinism, previous episodes of hypoglycaemia, respiratory, cardiac, metabolic and neurological disorders, or cerebrovascular abnormalities, the propranolol starting, maintenance and incremental dose schedules may need to be modified with a typical starting dose of 0.5 mg/kg daily. **Segmental haemangiomas including PHACES syndrome** (posterior fossa malformations–haemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe): This group of patients pose a distinctive treatment challenge, as they frequently require prompt treatment for airway and periocular IH, but propranolol may increase the haemodynamic risks associated with an otherwise asymptomatic cerebral arteriopathy in this group. **Treatment duration:** Treatment of IH should extend beyond the proliferative period of IH to avoid rebound growth. Premature cessation of propranolol may lead to rebound growth. In most patients the treatment can be safely stopped at 12–14 months of age.[4]

References	
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