Propranolol

Newborn use only

2019

Alert	**For dosing on infantile haemangiomas – please refer to "Propranolol for Infantile Haemangioma" formulary.** For infants with comorbidities that are likely to lead to hypoglycaemia (e.g. hyperinsulinism/preterm/low weight) – dose schedule needs to be cautious. Ensure infant has adequate enteral or parenteral nutrient intake.
Indication	Supraventricular and ventricular tachycardia Prevention of hypercyanotic episodes in unrepaired Tetralogy of Fallot Hypertrophic cardiomyopathy Systemic hypertension Thyrotoxicosis – treatment of sympathetic overactivity Phaeochromocytoma (with an alpha-blocker) Retinopathy of prematurity (not recommended) Infantile haemangioma – Please refer to "Propranolol for Infantile Haemangioma" formulary.
Action	Beta-blockers competitively block beta-adrenoceptors in heart, peripheral vasculature, bronchi, pancreas, uterus, kidney, brain and liver. Beta-blockers reduce heart rate, blood pressure (BP) and cardiac contractility; also depress sinus node rate and slow conduction through the atrioventricular (AV) node and prolong atrial refractory periods.
Drug Type	Beta-adrenergic blocker
Trade Name	Deralin, Inderal tablets, Hemangiol, Propranolol Auspman
Presentation	Deralin, Inderal, tablet 10 mg, 40 mg Deralin tablet 160 mg Propranolol (Auspman) 2 mg/mL Oral Solution Hemangiol 3.75 mg/mL Oral Solution Propranolol suspension (formulas for multiple concentrations exist) compounded by Pharmacy Department
Dosage / Interval	**Cardiac conditions and hypertension:** Commence at 0.5–1 mg/kg/dose* 8 hourly and increase to 1–2 mg/kg/dose 8 hourly once dose tolerated. *For infants with comorbidities that are likely to lead to hypoglycaemia (e.g. hyperinsulinism/preterm/low weight) – commence at 0.5 mg/kg/dose 8 hourly and increase to 1–2 mg/kg/dose 8 hourly as tolerated. **Thyrotoxicosis:** 1–2 mg/kg/day in 2–3 divided doses to be titrated to heart rate and in consultation with endocrinologist/cardiologist. **Phaeochromocytoma**: See evidence review. **Retinopathy of prematurity**: See evidence review.
Maximum daily dose	Hypertrophic cardiomyopathy – doses as high as 5 mg/kg/dose 8 hourly may be used.
Route	Oral
Preparation/Dilution	
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	Heart rate and blood pressure for 2 hours after initiation or dose increases. Bradycardia: newborns (<1 month old) <70 beats per minute; infants (1–12 months old) <80 beats per minute. Blood glucose levels in premature infants and during intercurrent illness, especially in the setting of restricted oral intake.
Contraindications	Shock (cardiogenic and hypovolaemic). Bradycardia (45–50 beats/minute), second or third-degree AV block, sick sinus syndrome (without pacemaker), severe hypotension or uncontrolled heart failure.
Precautions	Consider discontinuing propranolol during intercurrent illness, especially in the setting of restricted oral intake, to prevent hypoglycaemia. 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 cause bradycardia, AV blocks and hypotension via their synergistic negative chronotropic effect. β-Blockers and non-dihydropyridine calcium channel blockers (diltiazem, verapamil) cause bradycardia, asystole, sinus arrest due to their additive effect on the heart. β-Blockers and digoxin cause bradycardia and AV block via their additive effect. β-Blockers and dronedarone cause bradycardia as both drugs slow heart rate and dronedarone can inhibit CYP2D6 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 (citalopram, escitalopram) cause bradycardia, AV blocks and hypotension can occur with fluoxetine and paroxetine which are potent inhibitors of CYP2D6 and thus slow metabolism of some β-blockers. Increased 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. Decreased blood levels/decreased 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 Oral Solution: 2-year shelf life. Refer to expiry on bottle. Hemangiol Oral Solution: Use within 2 months of opening. Compounded suspension from Pharmacy Department: Shelf life usually 30 days. Refer to expiry on bottle.
Storage	Do not freeze. Protect from light. Auspman Oral Solution: Store below 30°C. Hemangiol Oral Solution: Store below 30°C. Do not freeze. Protect from light. 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	**Efficacy:** **Prevention and treatment of retinopathy of prematurity in preterm infants:** A systematic review [4] found 3 RCTs (participants = 366), with all studies comparing oral propranolol with placebo or no treatment for prevention of ROP. Filippi et al 2013 [5] compared oral propranolol 1 to 2 mg/kg/day versus no treatment. Propranolol was administered until complete retinal vascularisation and for a maximum of 90 days. Korkmaz et al 2017 [6] compared propranolol 2 mg/kg/day or placebo from 31 weeks' PMA (duration not reported). Sanghvi et al 2017[7] compared oral propranolol 1 mg/kg/day or placebo (calcium carbonate 1 mg/kg/day) from 7 days of life and continued until complete retinal vascularisation or 37 weeks' PMA. No trials assessed beta-blockers in infants with established stage 2 or higher ROP with plus disease. Meta-analysis of 3 trials (n = 366) found oral beta-blockers reduced risk of requiring anti-VEGF agents (RR 0.32, 95% CI 0.12 to 0.86; I^2 = 0%; typical risk difference (RD) −0.06, 95% CI −0.10 to −0.01; I^2 = 75%; NNTB 18, 95% CI 14 to 84) and laser therapy (RR 0.54, 95% CI 0.32 to 0.89; typical RD −0.09, 95% CI −0.16 to −0.02; I^2 = 31%; NNTB 12, 95% CI 8 to 47). Meta-analysis of 2 trials (n = 161) found a reduction in progression to stage 3 ROP (typical RR 0.60, 95% CI 0.37 to 0.96; I^2 = 0%; typical RD −0.15, 95% CI −0.28 to −0.02; I^2 = 73%; NNTB 7, 95% CI 5 to 67). There was no significant effect of oral beta-blockers on progression to stage 2 ROP with plus disease or to stage 4 or 5 ROP. Although meta-analysis did not indicate a significant effect of beta-blockers on arterial hypotension or bradycardia, propranolol dosage in one study was reduced by 50% in infants of less than 26 weeks' gestational age due to severe hypotension, bradycardia, and apnoea in several participants. Analyses did not indicate significant effects of beta-blockers on complications of prematurity or mortality. None of the trials reported on long-term visual impairment. ***Conclusion:*** Limited evidence of low-to-moderate quality suggests that prophylactic administration of oral beta-blockers might reduce progression to stage 3 ROP and decrease the need for anti-VEGF agents or laser therapy. The clinical relevance of those findings is unclear as no data on long-term visual impairment were reported. Adverse events attributed to oral propranolol at a dose of 2 mg/kg/d raise concerns regarding systemic administration of this drug for prevention of ROP at the given dose. There is insufficient evidence to determine the efficacy and safety of beta-blockers for prevention of ROP. [LOE I GOR D] **Heart failure:** Two clinical trials have reported use of propranolol in infants with heart failure from congenital heart disease with left to right shunts [8, 9]. Buchhorn et al 2001 [9] compared propranolol 1 to 2 mg/kg/day + digoxin and diuretics (n = 10) versus digoxin and diuretics alone (n = 10) and reported propranolol improved the Ross heart failure score, lowered renin levels and lowered mean heart rates, whilst digoxin and diuretic treated infants had unchanged mean heart rate, less decrease of symptoms and a significant increase of renin levels. Ahuja et al 2013 [8] compared propranolol 1 to 2 mg/kg/day + diuretics and digoxin (n = 40) versus diuretics and digoxin (n = 40) in infants with ventricular septal defect and congestive heart failure. Fourteen (35%) patients in the conventional arm and 10 (25%) in the beta-blocker arm reached the primary endpoint (composite endpoint of death, hospitalisation and referral for surgery). Worsening of heart failure occurred more commonly in the conventional treatment arm compared to the propranolol arm (27.5 vs 5%; p = 0.015). Two patients in the conventional treatment arm and one patient in the propranolol arm died. No episodes of bradycardia or bronchospasm were reported with propranolol treatment. A systematic review [10] of beta-blockers for congestive heart failure included 7 studies (420 paediatric participants). Aetiologies of heart failure and beta-blocker varied between studies. Participants had a background of dilated cardiomyopathy in 3 trials, and congenital heart disease in 5 trials. Two trials (Ahuja 2013; Buchhorn 2001) investigated propranolol; Ghader 2009 studied metoprolol, and 4 trials carvedilol (Azeka 2002; Huang 2013; Ontoseno 2014). No difference in mortality and heart transplantation rates were reported between beta-blocker and control groups in 3 trials (Ahuja 2013; Azeka 2002; Shaddy 2007). An improvement in heart failure was reported in 4 trials (Ahuja 2013;

	Azeka 2002; Buchhorn 2001; Huang 2013); although an improvement could not be shown in a larger trial of carvedilol that included 161 children aged 3 months to 17 years (Shaddy 2007). No severe adverse events were reported the studies, apart from one episode of complete atrioventricular block. There was a small improvement in echocardiographic parameters LVEF and LVFS (Azeka 2002; Huang 2013; Shaddy 2007). ***Conclusion:*** There is not enough evidence to support or discourage the use of beta-blockers in children or to propose a paediatric dosing scheme. However, the existing data suggest that children with congestive heart failure might benefit from treatment with beta-blockers.[10] [LOE I GOR C] **Supraventricular tachycardia:** A single RCT and 2 cohort studies have reported the effects of pharmacological treatment of SVT in infants and children. Sanatini et al 2012 [11] in a RCT of 61 infants <4 months with SVT (atrioventricular reciprocating tachycardia or atrioventricular nodal re-entrant tachycardia excluding Wolff-Parkinson-White) compared digoxin (loading dose 30 micrograms/kg/day, maintenance 10.5 micrograms/kg/day) versus propranolol 0.5 mg/kg as a single dose then 1.0 mg/kg/dose 8 hourly. SVT recurred in 19% of patients on digoxin and 31% of patients on propranolol (P = 0.25). No first recurrence occurred after 110 days of treatment. The 6-month recurrence-free status was 79% for patients on digoxin and 67% for patients on propranolol (P = 0.34), and there were no first recurrences in either group between 6 and 12 months. There were no deaths and no serious adverse events related to study medication. Hornik et al 2014 [12] in a retrospective cohort of infants with SVT from the Pediatrix Medical Group neonatal ICU database compared 342 infants exposed to digoxin versus 142 infants exposed to propranolol. The incidence rate of treatment failure was 6.7/1,000 infant-days of exposure to digoxin and 15.4/1,000 infant-days of exposure to propranolol. Treatment failure was higher on propranolol when compared with that on digoxin (adjusted hazard ratio, 1.97; 95%CI 1.05–3.71). Hypotension was more frequent during exposure to digoxin versus propranolol (39.4 vs 11.1/1,000 infant-days; p <0.001). There was no difference in frequency of other clinical adverse events. Bolin et al 2017 [13] reported a retrospective cohort of infants with SVT from the Pediatric Health Information System database admitted at ≤2 days of age with structurally normal hearts and treated with an antiarrhythmic medication. 2,657 neonates were identified with a median gestational age of 37 weeks (interquartile range 34 to 39). Digoxin and propranolol were most commonly prescribed; digoxin use steadily decreased to 23% of antiarrhythmic medication administrations over the study period, whereas propranolol increased to 77%. Multivariable comparisons revealed that the odds of mortality for neonates on propranolol were 0.32 times those on digoxin (95% CI 0.17 to 0.59; p <0.001). Propranolol for the neonate with SVT is associated with lower in-hospital mortality and hospital costs compared with digoxin. ***Recommendation:*** ANZCOR recommendation for pharmacological management of specific dysrhythmias in the paediatric advanced life support guideline recommend adenosine as the drug of choice for SVT. Amiodarone may be used to treat haemodynamically stable or unstable SVT. Alternative drugs are procainamide, digoxin, a beta blocker or a calcium channel blocker. Calcium channel blockers should not be used to treat SVT in infants and should be avoided or used cautiously in children because they may induce hypotension and cardiac depression.[14] EHRA-AEPC Pediatric Cardiac Arrhythmias Consensus suggested dose for oral prophylactic propranolol for SVT and VT in infants: Propranolol 1–3 mg/kg in 3 divided doses daily.[15] [LOE II GOR C] **Hypertension:** There are no clinical trials of antihypertensive use in newborn infants. In a retrospective survey of antihypertensive use in infants ≤32 weeks and ≤1500 g birth weight discharged from one of 348 neonatal intensive care units managed by the Pediatrix Medical Group, hydralazine was the most commonly prescribed antihypertensive drug (1280/2504, 51%), followed by the angiotensin converting enzyme inhibitors captopril (734/2504, 29%) and enalapril (457/2504, 18%) (Table 3). Propranolol was the most commonly used adrenergic receptor blocker (380/2504, 15%) while amlodipine was the most commonly

	used calcium channel blocker (193/2504, 8%). [16] In adults with hypertension, a systematic review found 13 RCTs that compared beta-blockers to placebo (4 RCTs, 23,613 participants), diuretics (5 RCTs, 18,241 participants), calcium-channel blockers (CCBs: 4 RCTs, 44,825 participants), and renin-angiotensin system (RAS) inhibitors (3 RCTs, 10,828 participants). The most common beta-blocker reported was atenolol. Initiating treatment of hypertension with beta-blockers leads to modest CVD reductions and little or no effects on mortality. These beta-blocker effects are inferior to those of other antihypertensive drugs. ***Recommendation:*** In a review of treatment of hypertension in paediatric patients, beta-blockers are not considered first-line management. If used, dosage recommendations were: Propranolol: Initial: 1–2 mg/kg/day up to 80 mg/day; Maximum: 4 mg/kg/day up to 640 mg/day; given in 2 to 3 divided doses.[17] (LOE IV GOR B] **Safety:** β-adrenoceptor blockers are considered to be quite safe in recommended doses mainly because of their large therapeutic indices. One of their indications is chronic heart failure with reduced ejection fraction. However, their introduction may cause transient worsening of heart failure symptoms (e.g. too fast up-titration) due to their negative inotropic action. The initiation of treatment is recommended after stabilisation of heart failure symptoms. An increased risk of toxicity can be also the result of interactions with other drugs (see drug interactions). The manifestations of β-blocker overdose include bradycardia, atrioventricular (AV) blockade, hypotension, left ventricular failure and cardiogenic shock.[18] Reported adverse effects of oral propranolol include hypoglycaemia, bradycardia, hypotension, bronchospasm, sleep disturbance and gastrointestinal disorders. [1, 4] In clinical trials of propranolol versus placebo for prevention of ROP in preterm infants, there was no significant difference in arterial hypotension, bradycardia or bronchospasm requiring treatment or hypoglycaemia (glucose level <2.5 mmol/L). However, the only infants with these adverse events in the included trials received propranolol. Propranolol dosage in one trial (Filippi at al 2013 [5]) was reduced by 50% in infants of less than 26 weeks' gestation due to severe hypotension, bradycardia and apnoea in several extremely preterm infants. Meta-analysis from two trials did not indicate an effect of prophylactic oral beta-blockers on mortality or complications of preterm birth. [4] Meta-analysis of clinical trials of propranolol versus placebo for infantile haemangiomas found there was no significant difference in these serious adverse effects (5.3% versus 3.6% respectively).[1] **Tetralogy of Fallot cyanotic spells:** A review of case series of patient with tetralogy of Fallot cyanotic spells found 4 of the 6 case reviews reported a decrease in the number of recurring cyanotic spells in at least 66% of the participants following introduction of beta-blockers. Side effects reported included bradycardia, wheezing and death. [19] There was insufficient dosage reporting, but one study of 35 patients between the ages of 2 and 30 months receiving propranolol between 2.0 and 4.0 mg/kg/day reported treatment was successful in 80%.[20] [LOE IV GOR D] **Phaeochromocytoma:** This is rare in infants. Case series describe successful pre-operative management of hypertension with a sequential combination of phenoxybenzamine (alpha-blocker) (0.2 to 4 mg/kg/day) and propranolol (1 to 10 mg/kg/day).[21, 22] **Neonatal thyrotoxicosis:** Beta-blockers (propranolol 2 mg/kg/day divided in 2 doses for 1–2 weeks) are effective at controlling the symptoms such as tachycardia, hypertension, and poor feeding.[33] Other suggested regimens included 8-hourly doses.[34-37] **Pharmacokinetics/pharmacodynamics:** Propranolol is highly lipophilic and undergoes first-pass metabolism by the liver with only ~25% of oral propranolol reaching the systemic circulation. Multiple pathways in the cytochrome P450 system are involved in propranolol's metabolism.[23]

	Filippi et al 2013 [24] reported pharmacokinetic parameters at steady state in newborns treated with 0.5 mg/kg 6 hourly. The maximal (71.7 ± 29.8 ng/mL), minimal (42.2 ± 20.8 ng/mL) and average concentration (60.8 ± 25.0 ng/mL), time of maximal concentration (2.6 ± 0.9 hour) and area under the time-concentration curve (364.7 ± 150.2 ng/mL/hour) were similar to those observed in adults. In both dosing groups, elimination half-life was significantly longer (14.9 ± 4.3 and 15.9 ± 6.1 hours) and apparent total body clearance (27.2 ± 13.9 and 31.3 ± 13.3 mL/kg/min), lower than reported in adults, suggesting a slower metabolism in newborns. No differences were observed between newborns with different gestational age or different sex.
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Original version Date: 15/04/2019	**Author: NMF Consensus Group**
Current Version number: 1	**Current Version Date:** 15/04/2019
Risk Rating: Low	**Due for Review: 15/04/2024**
Approval by: As per Local policy	**Approval Date:**

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