Atenolol
For Infantile Haemangioma

Newborn use only

2022

Alert	
Indication	Infantile haemangioma (IH)
Action	Exact mechanism is unclear. Beta blockers inhibit the proliferation and induce the regression of the lesion during the proliferative phase. (1) Beta blockers (propranolol and atenolol) are racemic mixtures and are composed of 1:1 R (+) and S (-) enantiomers. S (-) has the beta blocker activity whereas R (+) enantiomer has no beta blocker activity. R(+) enantiomer component inhibits haemangioma stem cell (HemSC) differentiation to vessel formation.(2)
Drug Type	Cardio-selective β1-blocker.
Trade Name	Atenolol-AFT oral liquid; suspension prepared by pharmacy,
Presentation	5mg/mL oral liquid 2mg/mL oral suspension, prepared in-house by pharmacy
Dose	**Starting dose** <4 months of age: 0.5 mg/kg/dose TWICE DAILY*# ≥4 months of age: 1 mg/kg/dose ONCE DAILY. **Maintenance dose** <4 months of age: Starting dose can be continued or increased to 0.75 mg/kg/dose TWICE DAILY if no response in 1-2 weeks. * ≥4 months of age: Starting dose can be continued or increased to 1.5 mg/kg/dose ONCE DAILY if no response in 1-2 weeks. * **Treatment duration** Treatment can be stopped at 1 year of age and the majority of patients do not need treatment beyond 17 months of age. It can be ceased temporarily if required during inter-current illness. *Suggested twice daily regimen and dose increment is based on ANMF expert consensus as the data in preterm and neonates are very limited. Twice a day regimen is to avoid any potential adverse effects with a larger single daily dose. #In outpatient settings where close monitoring may not be possible, starting dose for neonates can be 0.5 mg/kg/dose ONCE A DAY (morning).
Dose adjustment	Therapeutic hypothermia – Not applicable. ECMO – No information. Renal impairment (3)– GFR 30-50 mL/min/1.73m^2 – Maximum 1 mg/kg every 24 hours. GFR <30 mL/min/1.73m^2 – Maximum 1 mg/kg every 48 hours. Hepatic impairment - Not applicable.
Maximum dose	2 mg/kg/day in unresponsive cases.(4, 5)
Total cumulative dose	
Route	Oral
Preparation	Oral liquid, oral suspension.
Administration	Administer with feeds.
Monitoring	Prior to commencement of therapy • Cardiovascular and respiratory examination is required before starting atenolol (auscultation, peripheral pulses, abdominal examination for potential liver enlargement) • Pre-treatment ECHO in selected cases (e.g., segmental haemangioma) • Pre-treatment ECG in selected cases (e.g., cardiac arrhythmias, segmental haemangioma) • Paediatric cardiology assessment in selected cases. • Baseline blood glucose needs to be checked only in patients at risk of hypoglycaemia. After first dose

	• Post-first dose monitoring is not routinely required. • If required, heart rate and blood pressure should be measured every 30 minutes for 2-4 hours. • Blood glucose level is to be checked only in patients at risk of hypoglycaemia (preterm, low birthweight, inter-current illness, faltering growth, neonates, history of hypoglycaemia). <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. • Heart rate and blood pressure measurement between appointments are not required if infant is well. <u>Stopping atenolol</u> Temporary cessation may be required if significantly reduced oral intake of feeds (due to risk of hypoglycaemia)
Contraindications	Relative Bronchospasm Congestive heart failure 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 atenolol
Precautions	Infants with comorbidities that are likely to lead to hypoglycaemia: Inter-current illness, preterm, low birthweight, infants at risk of hypoglycaemia. Hypoglycaemia: May mask signs of acute hypoglycaemia (e.g., tachycardia, tremor). They may also increase the incidence and severity of hypoglycaemia but data are conflicting. Cardiac failure: May precipitate cardiac failure. (6) First degree heart block: May worsen first-degree AV block. Peripheral circulation: May impair peripheral circulation and exacerbate symptoms of peripheral arterial disease. Hyperthyroidism: May mask clinical signs, e.g., tachycardia. Phaeochromocytomas: —May aggravate hypertension. Anaphylaxis: May reduce the response to adrenaline (epinephrine) for anaphylaxis. Myasthenia symptoms: May worsen. Anaesthesia and the peri-operative period: May have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be made aware of beta-blockade because of the potential for interactions with other drugs.
Drug Interactions	Calcium antagonists: (e.g., verapamil, diltiazem) – concomitant therapy may cause hypotension, bradycardia and asystole. Extreme caution is required.(6) Class IA and III anti-arrhythmic drugs may induce negative inotropic effect.(6) Clonidine: Concurrent use should be avoided because of the risk of severe withdrawal symptoms. If administered concomitantly, clonidine should not be discontinued until several days after the cessation of the beta-blocker.(6) Digitalis: Digitalis and beta-blockers are commonly used together. There have been reports of excessive bradycardia when beta-blockers are used to treat digitalis intoxication. (6) Sympathomimetic agents (e.g. adrenaline): Concomitant use may counteract the effects of beta-blockers.(6) Prostaglandin synthetase inhibitors (e.g. ibuprofen, indomethacin): Concomitant use may decrease the hypotensive effects of beta-blockers. (6)

Adverse Reactions	Gastrointestinal: constipation. Respiratory: bronchospasm. May respond to beta-2 stimulant. Biochemical: increase in AST, blood urea and creatinine Cardiovascular: bradycardia, hypotension, worsening of heart failure. Bradycardia may respond to atropine.
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Oral liquid: Use within 1 month of opening. (18) Oral suspension prepared by pharmacy: check with local pharmacy.
Storage	Oral liquid: store below 25°C. Protect from light. (18) Oral suspension prepared by pharmacy: check with local pharmacy.
Excipients	Oral liquid: sorbitol solution (70%) (non-crystallising), methyl hydroxybenzoate, propyl hydroxybenzoate, sodium saccharin, citric acid monohydrate, sodium citrate, propylene glycol and lemon line flavour PHL0132956. (18) Oral suspension: check with local pharmacy. Tablets (use to compound oral suspension): contents of excipients vary depending on brand.
Special Comments	
Evidence	**Background** Propranolol has been the gold standard agent for treatment of IH. However, propranolol has certain risks, including side effects of diarrhoea, hyperkalaemia, hypoglycaemia and bronchial hyperreactivity. Propranolol also affects the central nervous system (CNS) as it crosses the blood-brain barrier due to its lipophilic nature and may cause adverse reactions, including agitation and sleep disturbances.(7) In contrast, atenolol is a selective and hydrophilic β1-blocker with minimal effect on pulmonary β2 receptors (e.g. bronchospasm).(7, 8) Atenolol can be dosed once daily and does not cross the blood-brain barrier.(7-9) **Efficacy** Several systematic reviews have been published and reported similar findings: Atenolol was comparable to propranolol in terms of efficacy and in addition, atenolol was found to have similar or better safety profile.(7, 10-12) A meta-analysis by Liu et al analysed 8 studies including 608 participants. Only 2 of the studies were RCTs. Except for the response to medication (pooled OR=1.49; 95% CI, 0.85-2.18), all other outcomes (Haemangioma Activity Score (HAS), adverse reactions and relapse rate) were better for the atenolol group. Atenolol resulted in better HAS (pooled MD=0.16; 95% CI, - 0.42 to 0.73). Propranolol had more adverse reactions (pooled OR=2.17; 95% CI, 0.93-5.06) and a higher relapse rate (pooled OR, 1.67; 95% CI, 0.44-6.41), but these findings were not statistically significant. The results of this analysis suggest that atenolol may be non-inferior to propranolol and may offer advantages, including lower adverse reactions and relapse rates.(7) Another systematic review identified 7 studies (3 RCTs and 4 cohort studies) and found that propranolol resulted in a significantly higher rate of complete response compared to atenolol (85.4% vs 73.3%, P <.0004). However, there was a significantly greater number of adverse events in the propranolol group (P < .00001): 2.7 times higher odds of adverse events in the propranolol group.(12) A meta-analysis by Pattanshetti et al analysed 5 studies. Atenolol was comparable to propranolol in terms of HAS (mean difference 0.25, 95% CI; –0.21, 0.71) and complete response (OR =0.43; 95% CI; 0.17, 1.11; P = 0.08,). Atenolol was better than propranolol in terms of safety (OR = 0.11; 95% CI; 0.02, 0.51; P = 0.005) and wheezing/bronchial hyperreactivity (OR = 0.11; 95% CI; 0.02, 0.51; P = 0.005).(10) A systematic review by Wang et al analysed 9 studies including 341 IH patients treated with atenolol. The pooled response rate of atenolol was 0.90 (95% CI: 0.85–0.93), and the rebound rate was 0.11 (95% CI: 0.08–0.16). Among the 341 patients, 44 patients were switched to atenolol from propranolol due to adverse events. The response rate of subsequent atenolol treatment was 90.9% (40/44). Regarding adverse events, 141 patients reported 177 episodes of adverse events, and the pooled rate was 0.26 (95% CI: 0.12–0.47). Gastrointestinal symptoms (e.g. constipation, diarrhoea and vomiting)

	were the most frequent (22.6%). Widely known propranolol-related adverse events, including hypoglycaemia, bronchospasm, bradycardia and hypotension, were not recorded with atenolol.(11) A multi-centre, randomized, controlled, open-label clinical non-inferiority trial compared propranolol and atenolol for the management of IH among 377 infants. Infants were enrolled between the ages of 5 and 20 weeks.(8) All infants received at least 6 months of treatment and were followed for 2 years. In the propranolol group, propranolol was initiated at a dosage of 1 mg/kg/day divided 3 times daily for 1 week, which was then increased to 2 mg/kg/day divided 3 times daily from week 2. In the atenolol group, atenolol was initiated at 0.5 mg/kg/day in a single dose for 1 week and then increased to 1 mg/kg/day in a single dose from week 2. In both treatment groups, the treatment was tapered and discontinued on complete or nearly complete resolution of IH or if no further improvement of IH was observed after month 6. Atenolol resulted in a similar incidence of any response at month 6 (93.7% in the propranolol group vs 92.5% in the atenolol group; difference, 1.2%; 95% CI, −4.1% to 6.6%). At 24 months of age (week 96), in the propranolol group, 82.1% of these patients had a complete/nearly complete response, whereas 79.7% had a complete/nearly complete response in the atenolol group. Rebound growth rate that required an additional course of β-blocker therapy was 8.2%.(8) Another small RCT involving 1 -15 month old children (total=23) compared atenolol and propranolol for the management of IH. Patients treated with atenolol had a complete response of 53.8% and 60% with propranolol, respectively. These results were nonsignificant (P = .68).(13) <u>Atenolol and hepatic haemangioma in a preterm neonate:</u> There is a case report of an infant of 8-weeks adjusted age born at 24 weeks gestation with multiple cutaneous infantile hemangiomas and hepatic hemangiomas. Atenolol was commenced at 0.25 mg/kg twice daily, which was then increased to 0.5 mg/kg twice daily after 1 week. Sonography at week 18 did not identify any hepatic lesions. At week 19, the infant showed appreciable diminution of the cutaneous hemangiomas. At week 28, the dose was changed to 1 mg/kg/day once daily. At 12 months, atenolol was ceased without recurrence of the hemangiomas.(14) **Dose:** In most studies, atenolol regimen involved a single dose of 1 mg/kg/day.(8, 13, 15-17). One study administered a twice-daily dose of 1 mg/kg/day (4) and one study administered a single dose of 2 mg/kg/day.(5) **PHACE syndrome:** Use of beta blockers in patients with PHACE (posterior fossa malformations, haemangioma, arterial anomalies, cardiac defects, eye anomalies) syndrome has been debated owing to concerns that the cardiovascular effects of the drug may increase the risk for arterial ischemic stroke. However, a recent multicentre, retrospective cohort study supports the safety of oral propranolol in this patient population. ANMF expert consensus is the outcome report of this study can be extrapolated to atenolol.(18) **Safety** In the RCT by Ji et al, during the 8 hours after the initial propranolol or atenolol treatment and after the first dose adjustment, decreases in heart rate and blood pressure were not clinically significant. No significant differences in the mean blood glucose levels were observed between the 2 groups.(8) Systematic reviews reported that atenolol was well tolerated and demonstrated a better safety profile compared to propranolol. (7, 10-12) **Pharmacokinetics** Blood levels peak 2-4 hours after ingestion. There is no hepatic metabolism and the main route of elimination is renal excretion.(6) In patients with impaired renal function, there is progressive prolongation of the half-life.
Practice points	
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