Prescribing propranolol for infants at risk of anaphylaxis

Cathal O’Connor¹, Juan Trujillo², and Murphy M¹

¹South Infirmary Victoria University Hospital
²University College Cork

June 16, 2023

DR CATHAL O’CONNOR ORCID 0000-0001-7084-5293
DR JUAN TRUJILLO ORCID 0000-0001-6369-6218
PROF MICHELLE MURPHY ORCID 0000-0003-2431-076X

Prescribing propranolol for infants at risk of anaphylaxis

C O’Connor, ¹, ³ J Trujillo, ², ³, ⁴ M Murphy ¹, ⁵

¹ Dermatology, South Infirmary Victoria University Hospital, Cork, Ireland
² Paediatric Allergy, Cork University Hospital, Cork, Ireland
³ INFANT Research Centre, University College Cork, Cork, Ireland
⁴ HRB Clinical Research Facility Cork (CRF-C), University College Cork, Cork, Ireland
⁵ Medicine, University College Cork, Cork, Ireland

Corresponding author: Dr Cathal O’Connor, cathal.oconnor@ucc.ie

Word count: 749

Table/figure count: 2

Reference count: 10

Ethical Approval: N/A

Conflict of interest: None

Funding: None

Data availability: Data available publicly

Summary

Theoretical interactions between propranolol and epinephrine should not preclude their co-prescription in infants with complex infantile hemangiomas and severe food allergy.

Keywords

Food allergy; Anaphylaxis; Epinephrine; Adrenaline; Infantile hemangioma: Propranolol; Beta blocker

To the Editor,

A 6-month-old infant develops perioral erythema and urticaria immediately after ingestion of peanut butter and is prescribed epinephrine (adrenaline) auto-injectors. The baby is also on oral propranolol to treat
an infantile hemangioma (IH) on the upper eyelid. The pharmacist says that this combination is contraindicated due to the theoretically opposing effects of epinephrine and propranolol. What should the allergist-dermatologist dyad do in this scenario?

IH is the most common tumour in infancy, affecting 5-10% of infants, with 20% representing complex IH eligible for oral propranolol therapy due to risk of functional impairment or disfigurement. Food allergy (FA) is also very common in childhood, affecting up to 8% of children in the US, with 40% of those prescribed epinephrine auto-injectors. Given that both these common conditions typically develop in infancy, co-prescription of oral propranolol and epinephrine auto-injectors will be indicated in a considerable number of infants.

Epinephrine exerts its anti-anaphylactic effects via stimulation of the α- and β-adrenoceptors of the sympathetic nervous system, while propranolol is a non-selective β-blocker. α-adrenoceptor stimulation is responsible for vasoconstriction in the skin, mucosa, venous bed, and kidneys, resulting in increased peripheral vascular resistance and blood pressure. β-adrenoceptor stimulation is responsible for bronchodilation and vasodilation, especially in skeletal muscles, and increased heart rate and heart contractility, resulting in increased cardiac output. On this basis, there are two theoretical concerns about the use of propranolol and epinephrine concomitantly: that propranolol will blunt the response to epinephrine and cause refractory anaphylaxis; or that propranolol will lead to unopposed α-adrenoceptor stimulation and cause hypertension or bronchospasm (Figure 1). However, these concerns are referring to general pharmacodynamics and not pharmacodynamics during life-threatening anaphylaxis. There is no evidence that patients on β-blockers require increased doses of epinephrine for anaphylaxis. Acute hypertension is generally not a problem during anaphylaxis, and is particularly well tolerated in children. In many of the original case reports, patients on β-blockers with severe anaphylaxis had major cardiovascular disease, suggesting that their underlying cardiorespiratory dysfunction predisposed them to adverse outcomes, rather than medication.

In the event of anaphylaxis, it is essential that epinephrine is given as quickly as possible to optimize outcomes, and repeated if necessary. The only effective therapy for anaphylaxis is epinephrine, and this treatment should be utilized irrespective of β-blocker therapy. Emergency medical attention should always be sought in the event of anaphylaxis. If epinephrine is ineffective in treating anaphylaxis in infants on propranolol, then glucagon administration could be considered. Glucagon can reverse refractory bronchospasm and hypotension during anaphylaxis in patients on β-blockers by activating adenyl cyclase directly and bypassing the β-adrenergic receptor. Airway protection is important due to risk of emesis and aspiration with glucagon. Adding nebulized adrenergic and anti-muscarinic bronchodilator therapy may help if bronchospasm is not addressed with epinephrine.

Logistically, it is easier to keep young infants away from foods to which they are allergic, given that independent ambulation is uncommon under one year. Moreover, symptoms of food-induced anaphylaxis tend to be less severe in infants than in older children, usually manifesting as urticaria and vomiting, with remarkably less cardiorespiratory involvement. In addition, the maximum plasma concentration of propranolol is achieved 1-2 hours after administration, and the plasma half-life is 3-6 hours. Therefore, plasma levels will vary significantly over the course of the day, and may be below the threshold for having any effect on epinephrine at the time of anaphylaxis. Propranolol is also usually stopped at around one year of age due to the natural involution seen after this point, conveniently as children become more independent and inquisitive, and at higher risk of inadvertent exposure to allergens.

Propranolol is an exceptionally effective treatment for IH, and even more so when considering alternative treatments. Topical timolol has no effect on deep IH, and is ineffective in treating proliferative IH. Treatments prior to the advent of propranolol included potentially toxic treatments such as high dose oral corticosteroids, interferon α, and vincristine.

On the basis of this literature review, the authors have formulated guidance on management of propranolol prescription in infants with FA who require epinephrine auto-injectors (Table 1). As the prevalence of FA increases and the threshold for treating IH falls, the co-prescription of epinephrine autoinjectors and
propranolol is likely to increase. It is important to reflect on the low likelihood of needing to use epinephrine auto-injectors and the low likelihood of problematic interactions before stopping propranolol in otherwise healthy infants with FA.

Cathal O’Connor, MB
Juan Trujillo, MD MSc
Michelle Murphy, MB

From Dermatology, South Infirmary Victoria University Hospital, Cork, Ireland.

E-mail: Cathal.oconnor@ucc.ie

References


8 Waheeda Samady, Jennifer Trainor, Bridget Smith, Ruchi Gupta. Food-induced Anaphylaxis in Infants and Children. Annals of Allergy, Asthma & Immunology, 2018; DOI: 10.1016/j.anai.2018.05.025


Table

1 Review the genuine need for prescription of both medications
2 Consider dosing propranolol at the lower end of the recommended range eg 2mg/kg/day
3 Advise parents of the theoretical risk of interaction, explain the very low likelihood of risk, and discuss the risk: benefit ratio
4 Optimize avoidance strategies to prevent inadvertent exposure to allergenic foods
5 Educate parents on signs and symptoms of anaphylaxis
6 Educate parents on the indication and technique of epinephrine administration
7 Advise parents to attend an emergency department if anaphylaxis occurs
1 Review the genuine need for prescription of both medications
8 Consider glucagon therapy if insufficient response is seen to 2-3 epinephrine auto-injectors (medical staff)
9 Consider nebulised salbutamol and/or ipratropium if there is ongoing bronchospasm following 2-3 epinephrine auto-injectors

Table 1. Advice from the authors on management of infants who qualify for prescription or oral propranolol and epinephrine auto-injectors, based on a literature review.

Figure

Figure 1. Diagram of putative effects of propranolol and epinephrine on adrenoceptors.