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CLINICAL QUESTION

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Prescribing propranolol for infants at risk of anaphylaxis

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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 haemangioma (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 hypothetical scenario?

IH is the most common tumour in infancy, affecting 5%–10% of infants, with 12% representing complex IH eligible for oral propranolol therapy due to risk of functional impairment or disfigurement.[1] Food allergy (FA) is also very common in childhood, affecting 2.8% of infants under 1 year in the United States, with 40% of those prescribed epinephrine auto-injectors[2]; although many infants are not at high risk of anaphylaxis and most FA (e.g. cows' milk and hens' egg allergies) will resolve within the first year of life. Given that both these common conditions typically develop in infancy, co-prescription of oral propranolol and epinephrine auto-injectors will be indicated in a small 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.[3] α-adrenoceptor stimulation is responsible for vasoconstriction in the skin, mucosa, venous bed and kidneys, resulting in increased peripheral vascular resistance and blood pressure.[3] 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.[3] 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 a more severe anaphylaxis that is less responsive to epinephrine; 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.[4] Acute hypertension is generally not a problem during anaphylaxis[5] 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.[4]

In the event of anaphylaxis, it is essential that epinephrine is given as quickly as possible to optimize outcomes, and repeated if necessary. Epinephrine is universally recommended as first-line therapy for anaphylaxis, and this treatment should be utilized irrespective of β-blocker therapy.[3] Emergency medical attention should always be sought in the event of anaphylaxis. If there is a suboptimal response to epinephrine in an infant 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.[3] 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 present.[6]

Fatal outcomes from anaphylaxis in the first year of life are extremely rare, and symptoms of food-induced anaphylaxis tend

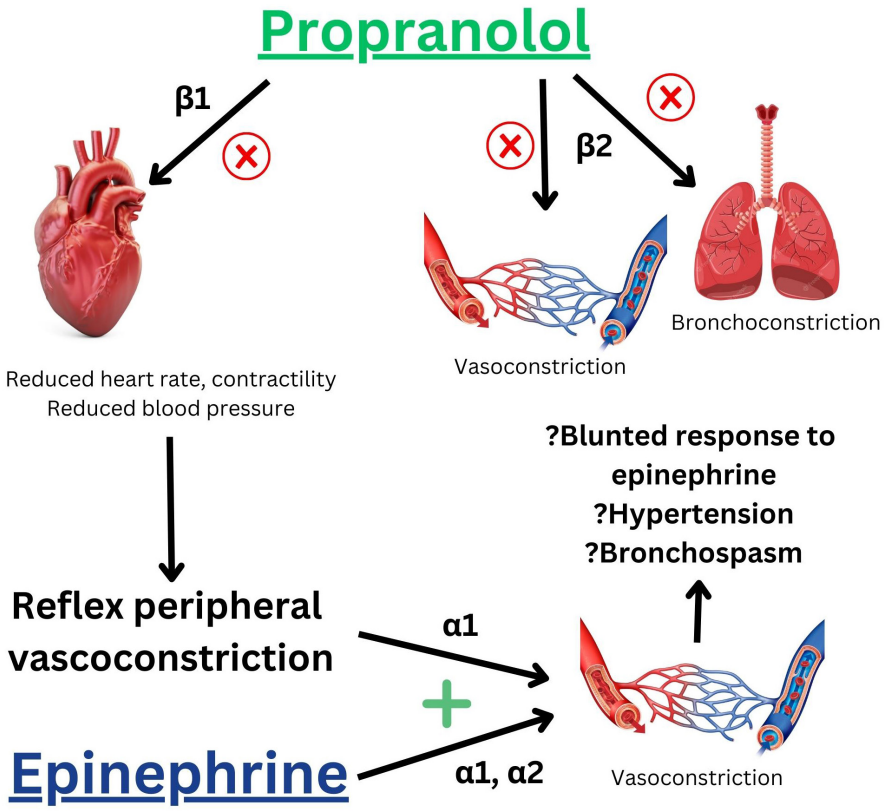

FIGURE 1 Diagram of putative effects of propranolol and epinephrine on adrenoceptors.

to be less severe in infants than in older children, usually presenting as urticaria and vomiting, with less cardiorespiratory involvement, but potentially more neurologic involvement (manifest as hypotonia).[7] Most anaphylactic reactions in infancy represent the first manifestations of food allergy, mainly due to cow's milk, and therefore occur before an epinephrine auto-injector has even been prescribed.[7] In addition, the maximum plasma concentration of propranolol is achieved 1–2 h after administration, and the plasma half-life is 3–6 h.[8] 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 1 year of age due to the natural involution seen after this point,[1] conveniently as children become more independent and inquisitive, and at higher risk of inadvertent exposure to allergens.[7] In Europe the recommended dose of epinephrine for infants weighing between 7.5 and 15 kg is 150 mcg, while in the United States the recommended dose is 100 mcg.[9]

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.[1]

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). These principles are also relevant for other instances where β-blockers are prescribed in children (e.g. for cardiovascular disease) in conjunction with epinephrine auto-injectors. As prescriptions for epinephrine auto-injectors for FA increase and the threshold for treating IH falls, the co-prescription of epinephrine auto-injectors 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.

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.

1. Review the genuine need for prescription of both medications
2. Consider dosing propranolol at the lower end of the recommended range eg 2 mg/kg/day
3. Advise parents of the theoretical risk of interaction, explain the very low likelihood of risk and discuss the risk: benefit ratio of different prescribing options
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 contact emergency services if anaphylaxis occurs
8. Consider glucagon therapy if insufficient response is seen to 2–3 epinephrine auto-injectors (medical staff)
9. Consider nebulized salbutamol and/or ipratropium as a second-line therapy if there is significant bronchospasm (medical staff)

AUTHOR CONTRIBUTIONS

COC conceived of the presented idea. COC, JT, and MM reviewed the literature on the topic. COC wrote the initial draft of the manuscript and created all figures/tables. COC, JT, and MM reviewed the manuscript and approved of its final version.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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