CASE REPORT

Efficacy of topical brimonidine-timolol for haemangioma of infancy and perils of off-label prescribing

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SUMMARY

We report three patients with superficial haemangiomas treated topically with Combigan ophthalmic solution (brimonidine 0.2%–timolol 0.5%), a combination selective α -2-adrenergic agonist and non-selective β -blocker Food and Drug Administration-approved for use in glaucoma. Topical brimonidine 0.2%–timolol 0.5% therapy improved the appearance of haemangiomas in all the cases. Two patients did not experience any adverse effects. One patient had hypothermic episodes which were initially thought to be because of brimonidine 0.2%–timolol 0.5% therapy. However, an episode occurred a few weeks after discontinuation and brimonidine 0.2%–timolol 0.5% therapy was ruled out as a cause. Despite the benefit, off-label use of brimonidine 0.2%–timolol 0.5% therapy served as a pitfall in the evaluation of an unusual constellation of worrisome symptoms. In conclusion, brimonidine 0.2%–timolol 0.5% therapy is a promising alternative in the topical treatment of haemangiomas. It may have synergistic effects and increased efficacy by targeting haemangiomas via two mechanisms (α -agonism and β -inhibition), but the risk of unforeseen adverse effects must always be considered when prescribing off-label treatment, especially in infants.

BACKGROUND

Haemangioma of infancy is the most common tumour of childhood, affecting 80 000 infants/year in the USA. There are currently no FDA (Food and Drug Administration)-approved treatments for this condition, but several case reports and molecular studies have documented the efficacy of β -blockers orally and topically. This report summarises the

clinical courses of three infants with superficial haemangiomas treated topically with Combigan ophthalmic solution brimonidine 0.2%–timolol 0.5% therapy, a combination selective α -2-adrenergic agonist and non-selective β -blocker FDA-approved for twice-daily use in glaucoma for patients down to age two. The combination product, brimonidine 0.2%–timolol 0.5% therapy, offers a potential synergistic effect for glaucoma, and was offered to our patients to target haemangioma growth via two mechanisms—the β -blocking effects of timolol and α -2-adrenergic effects of brimonidine on abnormal peripheral vasculature.

CASE PRESENTATION

Case 1

A 4-month-old Caucasian female born at 39 weeks gestation presented with a haemangioma first noted at 6 weeks of age. At that time the lesion was a 3 mm tense bright red, minimally elevated papule on the right alar rim (see figure 1A). A trial of brimonidine 0.2%–timolol 0.5% therapy was recommended, with instructions to use one drop twice daily, applied from a finger, and massaged into the haemangioma. At 2 months follow-up, no adverse effects were reported. The lesion measured 2 mm, was significantly lighter in colour and had no papular component (see figure 1B). The patient's mother was encouraged to continue twice daily brimonidine 0.2%–timolol 0.5% therapy and to anticipate further haemangioma fading.

Case 2

An almost 4-month-old Caucasian female, born after full-term pregnancy, presented with a

Figure 1 Right alar rim haemangioma. (A) Pretreatment. (B) Post-treatment: 2 months after topical treatment with brimonidine 0.2%–timolol 0.5% therapy. The lesion is smaller, lighter and flatter.

To cite: Chu MB, Searcy G, Siegfried E. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009365

Figure 2 Left wrist haemangioma. Pretreatment. A bright red, minimally elevated segmental plaque is seen: (A) dorsal aspect, pretreatment and (B) ventral aspect, pretreatment. Post-treatment: the plaque is much lighter, thinner and smaller: (C) dorsal aspect, post-treatment and (D) ventral aspect, post-treatment. Treatment was discontinued after 3 weeks of treatment; photo taken 2 months after cessation of treatment. Fading and regression continued even after discontinuation of brimonidine 0.2%-timolol 0.5% therapy.

haemangioma first noted at 1 week of age. At that time the lesion was a 4.7×4.0 cm bright red, minimally elevated segmental plaque on the left wrist without evidence of ulceration (see figure 2A, B). A trial of brimonidine 0.2%-timolol 0.5% therapy was recommended, with instructions to massage two drops into the haemangioma twice daily. This treatment was continued for 3 weeks, until the entire 5 ml bottle was used. The lesion reportedly flattened and faded with treatment, and remained unchanged off treatment. At follow-up 3 months later, the haemangioma was significantly improved (see figure 2C, D). There were no reported adverse effects. The patient's mother was provided with a refill to be used if the lesion developed evidence of growth or ulceration.

Case 3

A 3-month-old Caucasian male born at 30 weeks gestation presented with a haemangioma first noted at 2 weeks of age. At that time, the lesion was a 5 mm, tense, bright red, dome-shaped papule on the left medial infraorbital area. A trial of brimonidine 0.2%-timolol 0.5% therapy was recommended with instructions to massage one drop into the haemangioma twice daily, applied by fingertip. A recommendation was also given to occlude the right medial canthus during and for 1 min after application, to minimise the risk of ocular and nasal vestibule exposure.

Eight days after starting brimonidine 0.2%-timolol 0.5% therapy, the patient presented to the emergency department (ED) with lethargy, hypotonia and hypothermia. His axillary temperature measured at home was 94°F. In the ED, his rectal temperature was 94.9°F, blood pressure 101/48, pulse 141, respiratory rate 36, oxygen saturation 97% and glucose 96. The differential diagnosis included meningitis, sepsis, urinary tract infection, environmental hypothermia and non-accidental trauma. With warming, the patient became alert with normal tone, while an evaluation to rule out sepsis was initiated. He was admitted for additional evaluation and empiric parenteral antibiotics. Extensive workup was negative for evidence of infection and trauma. He was discharged after 3 days without additional treatment.

Twelve days later, about 3 weeks after starting brimonidine 0.2%-timolol 0.5% therapy, the patient was transported by ambulance to the ED after a spontaneously resolving, 7 min episode of unresponsiveness, hypotonia and pallor. His axillary

Figure 3 Left medial infraorbital area haemangioma. Photo taken after 3 weeks off brimonidine 0.2%-timolol 0.5% therapy. Haemangioma became lighter and smaller with 3 weeks of brimonidine 0.2%-timolol 0.5% therapy treatment, but was starting to regrow and darken off treatment.

temperature at home was 94.7°F and his rectal temperature was recorded at 97.5°F by the paramedics. In the ED his vital signs were: rectal temperature 97.6°F, blood pressure 109/37, pulse 131, respiratory rate 58, oxygen saturation 100% and glucose 94, and his level of responsiveness quickly returned to baseline without intervention. The patient was hospitalised, and extensive metabolic evaluation was unremarkable, including pyruvate, lactate, plasma amino acids, urine organic acids and acylcarnitine. When questioned, his mother stated that brimonidine 0.2%-timolol 0.5% therapy had occasionally been dropped directly onto the haemangioma from the bottle, and some medication may have run into his eyes, but she denied the possibility that medication was ingested. Brimonidine 0.2%-timolol 0.5% therapy was held owing to concerns that his presentation could have been a medication-related side effect.

Sixteen days after brimonidine 0.2%-timolol 0.5% therapy was discontinued, the patient suffered a third episode of lethargy and hypothermia (rectal temperature 96.8°F at home), that spontaneously resolved within 1 h. Repeat metabolic screening laboratory tests were not revealing, but the patient's mother mentioned she had been taking duloxetine and wondered if excretion of this drug into breast milk could be the cause of her son's symptoms.

One week later, 3 weeks off brimonidine 0.2%-timolol 0.5% therapy, the patient returned for dermatology follow-up. His mother reported that the lesion had flattened and faded while on brimonidine 0.2%-timolol 0.5% therapy but enlarged and darkened off treatment (see figure 3).

DISCUSSION

Combigan is an ophthalmic solution of brimonidine (0.2%) and timolol (0.5%) that was FDA approved in October 2007 to treat glaucoma or ocular hypertension in patients down to 2 years of age (Allergan, Inc, Irvine, California, USA).¹ Timolol ophthalmic solution (Merck & Co, Whitehouse Station, New Jersey, USA),² a non-selective β -blocker FDA-approved in 1978 to treat glaucoma has recently become a popular topical alternative to the more well-studied oral propranolol for the treatment of infantile haemangioma.^{3–14} Brimonidine is a selective α -2-adrenergic agonist FDA-approved in 1996 as a 0.1–0.2% ophthalmic solution for the treatment of glaucoma (Allergan).¹⁵ The potent vasoconstrictor effects of brimonidine prompted formulation of a 0.5% cream, as a topical treatment for acne rosacea.¹⁶ The combination product, brimonidine 0.2%-timolol 0.5% therapy, offers a potential synergistic effect for glaucoma,

and was offered to our patients to target haemangioma growth via two mechanisms—the β -blocking effects of timolol and α -2-adrenergic effects of brimonidine on abnormal peripheral vasculature.

Topical brimonidine 0.2%-timolol 0.5% therapy, improved the appearance of the haemangiomas for all the three infants. The haemangioma in case 1 was almost imperceptible following 2 months of topical application, while the segmental haemangioma in case 2 lightened after 3 weeks of treatment, and did not worsen for 3 months after discontinuation. The haemangioma in case 3 also responded well to treatment, although the beneficial effects were lost 3 weeks after discontinuation. Despite the benefit, off-label use of the combination drug served as a pitfall in the evaluation of an unusual constellation of worrisome symptoms.

Haemangioma of infancy is the most common tumour of childhood, affecting 80 000 infants/year in the USA.¹⁷ There are currently no FDA-approved treatments for this condition, but several case reports and molecular studies have documented the efficacy of β -blockers^{18–42} and an industry-sponsored, phase II/III international multicentre, placebo-controlled, double-blind trial of oral propranolol is in progress. Generic propranolol suspension has been available in the USA for decades, but the popularity of this off-label treatment for haemangioma of infancy is evidenced by a significant increase in prescriptions: 30 000 more written in 2011 than 2007.⁴³ Documented adverse effects of propranolol for paediatric haemangiomas include bronchospasm, cyanosis/cold extremities and low body temperature.⁴⁴ Recently, the fourfold more potent topical Timolol and as well as other β -blockers have become increasingly prescribed by primary care physicians and a variety of specialists, even as first-line therapy for haemangioma of infancy.²

This is the first report of topical brimonidine 0.2%-timolol 0.5% therapy as a treatment for haemangioma of infancy. Topical brimonidine (Allergan) as monotherapy and as combination brimonidine 0.2%-timolol 0.5% therapy, is FDA approved down to age two for the treatment of glaucoma.¹⁵ Recognised adverse effects include dizziness, fatigue, hypotension and infection.^{1 15} Postmarketing surveillance of these drugs in adults has included ocular complaints (5–15%) and somnolence (1–5%).^{1 15} Isolated case reports have documented apnoea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression and somnolence in infants following accidental ingestion.⁴⁵ Similar side effects have been reported in adults after increased exposure following cornea transplants.^{15 45}

The hypothermia, unresponsiveness and pallor that complicated treatment in case 3 were not likely related to topical brimonidine 0.2%-timolol 0.5% therapy, but illustrate an important pitfall in off-label treatment, especially in the vulnerable infant population. Although this patient's heart rate, blood pressure and pulmonary status were not compromised and his glucose level was normal, the drug was suspected as a diagnosis-of-exclusion. And given the very short pharmacologic half-lives both timolol and brimonidine (7 and 3 h, respectively), total washout would be expected after 35 h (5 half lives).^{2 15} However, only after our patient's third lethargic episode, 16 days off brimonidine 0.2%-timolol 0.5% therapy, be excluded as the most likely cause, and breast-milk exposure to duloxetine be considered. Duloxetine (Lilly USA, LLC, Indianapolis, Indiana, USA) is excreted into breast milk at 0.14% the concentration taken by the mother.⁴⁶ While this drug is not approved for use in breast feeding mothers, breast milk exposure has been associated with temperature instability, hypotonia and lethargy in nursing infants.⁴⁶

In conclusion, the combination of active ingredients in brimonidine 0.2%-timolol 0.5% therapy may have synergistic and increased efficacy in the topical treatment of haemangioma of infancy, but the risk of unforeseen adverse effects must always be considered when prescribing off-label treatment, especially in infants. Care should be taken to minimise risk of systemic absorption especially for periocular haemangiomas when using topical timolol or brimonidine 0.2%-timolol 0.5% therapy. Brimonidine 0.2%-timolol 0.5% therapy should optimally be applied to the lesion from a fingertip to minimise the risk of excess application and inadvertent intraorbital, lacrimal duct and nasal vestibule exposure. For treating periocular haemangiomas, we recommend that the eyelids be closed during application and that pressure be applied to occlude the medial canthus for 30–60 s during and after treatment. Brimonidine 0.2%-timolol 0.5% therapy may be a promising topical alternative for small superficial infantile haemangiomas, but additional studies are warranted.

Learning points

- ▶ There are currently no Food and Drug Administration-approved treatments for haemangiomas of infancy.
- ▶ The β -blockers orally and topically have been used off-label with success.
- ▶ Topical use of the combination ophthalmic solution, Combigan (brimonidine 0.2%/timolol 0.5%), may increase efficacy through a synergistic effect of targeting haemangioma growth via two mechanisms—the β -blocking effects of timolol and α -2-adrenergic effects of brimonidine on abnormal peripheral vasculature.
- ▶ The risk of unforeseen adverse effects must always be considered when prescribing off-label treatment, especially in infants, a vulnerable patient population.

Acknowledgements We thank the patients and families for their support.

Contributors All authors had a substantial contribution in all of the tasks listed: conception and design, acquisition of data or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version published.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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